

Syphilitic hepatitis: should it be added to the algorithm of hepatogram alterations? Report of three cases

Victoria Veloso, Daniela Chiodi, Nelia Hernández

Departament of Gastroenterology and Hepatology, Clinic Hospital. Montevideo, Uruguay.

Acta Gastroenterol Latinoam 2020;50(3):335-340

Recibido: 06/02/2020 / Aceptado: 17/07/2020 / Publicado online: 28/09/2020

Summary

Hepatic involvement due to syphilis is a rare manifestation where a high index of suspicion is required for its diagnosis. Three clinical cases of syphilitic hepatitis with cholestatic/mixed presentation are described and discussed, without criteria of severity and rapid biochemical response once the specific treatment has been administered.

Key words. Syphilis, hepatitis, cholestatic pattern.

Hepatitis sifilítica: ¿deberíamos agregarla al algoritmo de las alteraciones del hepatograma? Reporte de una serie de casos

Resumen

La afectación hepática de la sífilis es una manifestación poco común que requiere de un alto grado de sospecha para su diagnóstico. Se describen y discuten tres casos clínicos de he-

patitis sifilítica con la presentación colestásica o mixta, sin criterios de gravedad y con una rápida respuesta bioquímica una vez administrado el tratamiento específico.

Palabras claves. Sífilis, hepatitis, patrón colestásico.

Introduction

Syphilis is a sexually transmitted systemic infectious disease caused by *Treponema Pallidum*, with high prevalence in at-risk populations.^{1,2} Men who have sex with men (MSM) and those infected with human immunodeficiency virus (HIV) are the main risk groups. The most frequent route of transmission is sexual, and less commonly, oral.³ The progression of the disease is divided into three successive stages: the *primary stage*, characterized by the presence of the inoculation chancre, the *secondary stage*, characterized by mucocutaneous lesions and adenomegalies, and the *tertiary stage* where cardiological, ophthalmic, and auditory manifestations, as well as the presence of syphilitic gums are evident. In the absence of clinical manifestations, its diagnosis becomes extremely challenging.^{1,2}

Hepatic involvement is described in 0.2-3%, with higher prevalence in the secondary and tertiary stages as a result of the hematogenous dissemination of *Treponema*. In 90% of the cases there is an association with maculopapular rash in the torso and extremities and, in a smaller percentage, with genital symptoms (balanitis).³⁻⁹ The cholestatic pattern is the usual form of presentation, although mixed and necrotic forms have been reported.¹⁰ Positive results of the non-treponemal (VDRL or RPR)

Correspondencia: Victoria Veloso
Avenida Italia 2870. Montevideo, Uruguay
Correo electrónico: victoriavelosogiribaldi@gmail.com

and treponemal (FTA-ABS, ELISA) serological tests, associated with clinical and biochemical improvement with treatment, after exclusion of other more frequent etiologies, allows to confirm the diagnosis.³ Histology is not relevant and the most frequent findings are: periportal lymphocytic infiltrate, focal necrosis, non-caseifying granulomas and in a minority of cases, the presence of spirochetes.^{11, 12} Although resolution is usually the norm, cases of fulminant hepatic failure have been reported.¹³⁻¹⁴

The aim of presenting this series of cases is to communicate the hepatic manifestation of a disease known for several decades, which is considered infrequent, but is probably under-diagnosed.

Clinical cases

Case 1

A 43-year-old man, without risk factors for liver disease, who consulted for pruritus and choloria of a week of evolution. He had no abdominal pain or fever. Jaundice was found on physical examination, without other alter-

ations. The biochemical tests on admission showed: total bilirubin (BT) 2.4 mg/dl, direct bilirubin (BD) 2.1 mg/dl, alkaline phosphatase (AP) 3270 U/L (240), GGT 512 U/L (33), AST 186 U/L (27), ALT 395 U/L (33), Total protein test 6.9 g/dl, PT 82% (70-100), hemoglobin 13.4 g/dl, platelets 326,000/mm³, white blood cells 7.7 10³/uL (69% neutrophils, 15% lymphocytes, 3% eosinophils). Abdominal ultrasound and magnetic cholangioresonance (CRMN) excluded biliopancreatic pathology. Serology for hepatotropic viruses (IgM HAV, HBsAg, AntiHbc, AntiHBs, HCV ELISA), nonhepatotropics (CMV IgM, EBV IgM) and the autoimmunity panel (ANA, AMA, ASMA) were non-reactive. The electrophoretic proteinogram was normal and the HIV serology negative. Reactive TPHA and VDRL 1/64. Treatment with benzathine penicillin was initiated intramuscularly at a dose of 2,400,000 IU/ per week, with a total of 3 doses. The patient showed clinical improvement after treatment was established. At 24 weeks of the start of treatment, hepatogram normalization and serological negativization were observed (Chart 1A).

Chart 1. Biochemical evolution of clinical cases 1 (A), 2 (B), 3 (C). The values of AP, GGT, ALT and AST are represented in number of times over the normal value

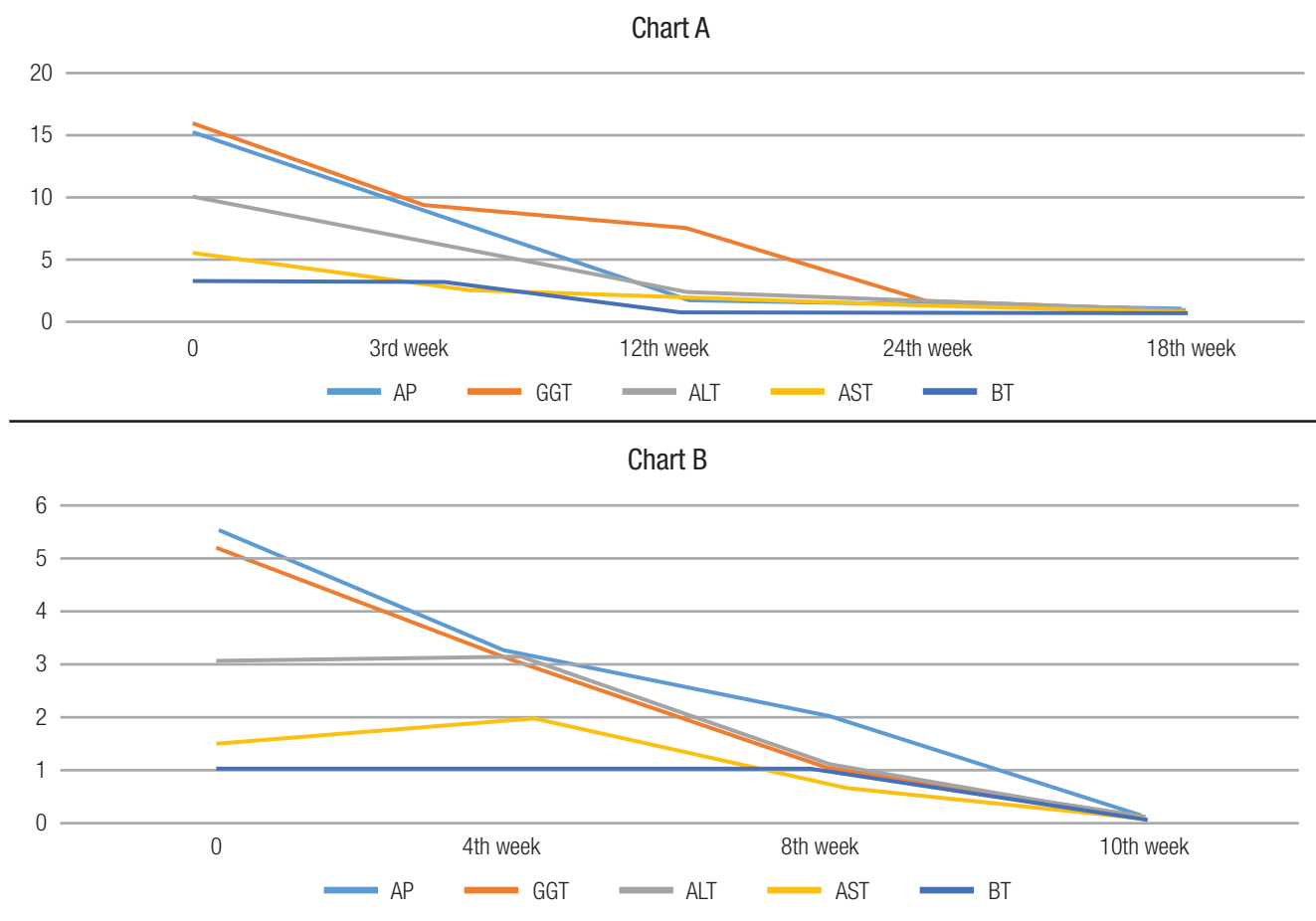
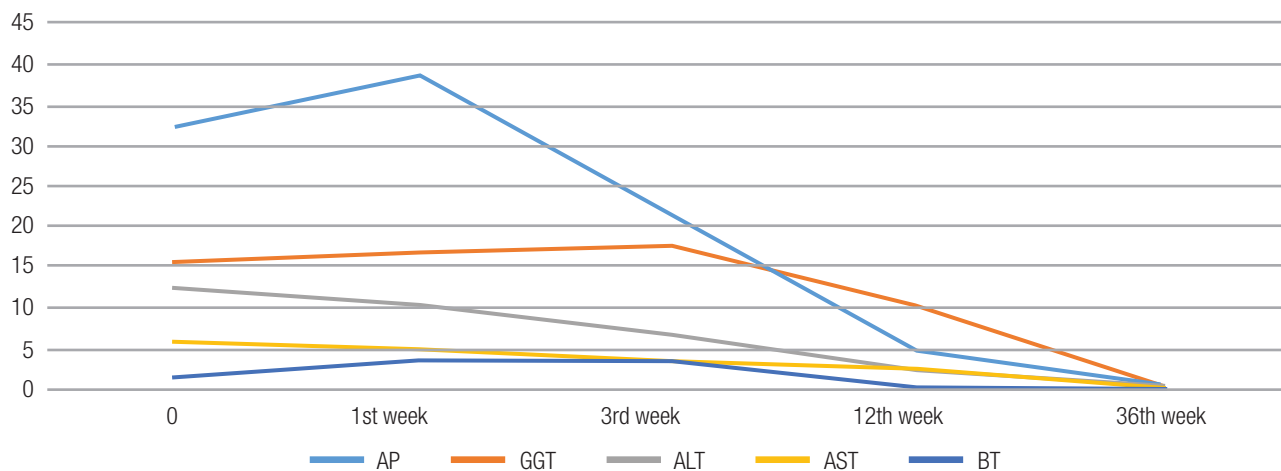


Chart C



Case 2

A 52-year-old man with a diagnosis of dyslipidemia and arterial hypertension, in treatment with atorvastatin and enalapril for 4 years. He consulted for pruritus, asthenia and adynamia of 2 weeks of evolution, without abdominal pain or fever. The examination showed hyperpigmented and pruritic macule lesions on the back of the arm and forearm (Figure 1).

Figura 1. Macular exanthema in forearm (case report 2)



Paraclinical tests showed: BT 2.8 mg/dl, BD 1.9 mg/dl, AP 646 U/L (240), GGT 219 U/L (33), AST 69 U/L (27), ALT 127 U/L (33), Total protein test 7.2 g/dl, PT

91% (70-100), hemoglobin 11.9 g/dl, platelets 458,000/mm³, white blood cells 6.8 10³/uL (70% neutrophils, 12% lymphocytes, 2.8% eosinophils). Ultrasound and computed abdominal tomography (CAT) with contrast excluded biliopancreatic pathology. HIV, IgM HAV, HBsAg, IgM AntiHbc, HCV ELISA, CMV IgM and EBV IgM as well as autoimmunity (ANA, ASMA, AMA) were ruled out. Electrophoretic proteinogram was normal. Positivity of the VDRL (1/256) and TPHA allowed for a diagnosis of syphilitic hepatitis. Treatment with intramuscular 2,400,000 IU Benzathine Penicillin was initiated, with clinical improvement and normalization of liver enzymes at 8 weeks (Chart 1B).

Case 3

A 39-year-old man with risky sexual behaviors and laparoscopic cholecystectomy for vesicular polyps in 2008. Routine examinations showed hepatogram abnormality. He was asymptomatic and the physical examination was normal. Paraclinical tests showed: BT 0.8 mg/dl, AP 725 U/L (240), GGT 449 U/L (33), AST 188 U/L (27), ALT 291 U/L (33). The serology of IgM HAV, HBsAg, AntiHbc IgM, HCV ELISA, CMV IgM and EBV IgM was negative. The HIV test was reactive and confirmed by viral load. Abdominal ultrasound showed no abnormalities. At 3 weeks the hepatogram showed: AP 3038 U/L (240), GGT 2194 U/L (33), AST 160 U/L (27), ALT 338 U/L (33). The serology for syphilis (VDRL 1/256 and TPHA) was positive and the treatment with Benzathine Penicillin 2,400,000 IU (3 doses) was initiated. 24 weeks after the initiation of the treatment, improvement of the hepatogram and the negativity of the serology were observed (Chart 1C).

Discussion

Syphilis is a sexually transmitted multisystemic disease that, despite being preventable and curable, constitutes a major health problem.⁵ It is known as “the great simulator” due to its various forms of presentation, in which pruritus, dermatological and genital manifestations are the most frequent.⁷ Hepatic involvement is rare and is generally considered in patients with risky sexual behavior after excluding other more frequent etiologies. The literature on syphilitic hepatitis is scarce and in the form of reports and case series.^{1-4, 6-25} There is only one systematic review in which 73 articles published between 1951 and 2017 were includ-

ed, with 144 cases of syphilitic hepatitis. The average age was 40.5 years, the predominant sex was male (90.3%), 54.4% of the patients were homosexual and 61.4% had HIV. Almost 90% (88.9%) was in the early stages of syphilis (primary or secondary). Rash was the most frequent symptom (77.9%), followed by fatigue, anorexia (56.7%) and jaundice (35.1%). The cholestatic pattern was the most predominant and in 38% of the cases a liver biopsy was performed. All patients received antibiotic treatment (89.5% penicillin) and showed a good response.²⁶

Table 1 describes the main characteristics of those reports and case series found in the literature and not included in the systematic review.

Table 1. Reports and case series not included in the systematic review

Author and year	No. of cases	Sex	Age	HIV/other STDs	Clinical manifestations	Pattern	Biopsy	VDRL TPHA	Status	Time to normalization
Rinascente 2015 ²	1	M	34	HBV resolved HIV -	Rash, cholestatic jaundice	Hepatocellular	Yes	1/64 +		12 weeks
		M	51	HBV- HIV-		Cholestatic	No	1/64	secondary	4-16 weeks
Mezzano ⁴	3	M	30	HIV + HBV +	Rash, low-grade fever, asthenia, edema, foamy urine	Cholestatic	No	1/128	secondary	5 weeks
		M	43	HBV- HIV-	Asthenia, fever, rash, pruritus	Mixed	No	1/16	secondary	4-16 weeks
Pizarro ⁶	1	M	34	HBV- HIV+	Asthenia, headache, fever, abdominal pain, jaundice, choluria	Cholestatic	Yes	+	secondary	
Tercero Lozano ⁸	1	M	46	HBV- HIV-	Abdominal pain, rash, jaundice, choluria, acholia	Cholestatic	No	1/320	secondary	
German ⁹	1	M	51	HBV- HIV+	Fatigue, jaundice, choluria, acholia	Cholestatic	Yes	+		12 weeks
Pizarrosa ¹⁰	1	F		HIV -	Fever, myalgia, headache, non-itchy rash	Cholestatic	No	+ 1/32	secondary	1 week
Affonso ¹³	1	F	18	HBV- HIV-	Epigastralgia, nausea, vomiting, rash, jaundice	Hepatocellular		1/512	secondary	Death
Suarez ¹⁷	1	M	40	HBV- HIV-	Asthenia, weight loss, anorexia, abdominal pain, jaundice	Cholestatic	Yes	+ 1/26	secondary	
Miguel Gomez ¹⁸	1	M	57	HIV -	Balanitis, asthenia, fever, jaundice, choluria	Cholestatic	No	1/1280	secondary	2 weeks
Murphy ²⁰	1	F	40	HIV -	Jaundice, rash	Cholestatic	Yes	+	secondary	4 weeks
Bronstein ²¹	1	M	15	HBV- HIV-	Jaundice, rash	Hepatocellular	No	+	secondary	8 weeks
Hussain ²²	1	M	37	HBV- HIV-	Abdominal pain, nausea, vomiting, jaundice	Mixed	Yes	1/64	secondary	
Tolia ²³	1	M	32	HBV- HIV+	Abdominal pain, fever, asthenia, rash	Cholestatic	No	1/64	secondary	
Huang ²⁴	1	M	47	HBV- HIV-	Jaundice, rash	Mixed	Yes	1/32	secondary	8 weeks
Horn ²⁵	1	M	47	-	Fatigue, abdominal pain, rash, nausea, weight loss	Cholestatic	No	1/512	secondary	8 weeks

In this series the average age was 44 years, all were men, with cholestatic/ mixed pattern and one of them had HIV. In HIV-infected patients the prevalence of syphilitic hepatitis is 0.2-10% of the cases and, in general, this infection is contemplated within the differential diagnoses of liver profile alterations in this subgroup.^{1, 15, 16}

Liver biopsy in syphilitic hepatitis is nonspecific and the presence of spirochetes can be difficult to demonstrate. Even in cases where immunohistochemistry or Warthin Starry staining was performed, the bacteria was found in 19 of the 28 cases.²⁶

Treponema pallidum still presents extreme susceptibility to penicillin, so much so that there are no reports of resistant syphilis.⁵ The current recommendation for the treatment of early syphilis (primary and secondary) is the administration of benzathine penicillin G 2.4 million IU, in 1 to 3 doses, with cure rates reported

between 80-95% at 6 months follow-up and normalization of the hepatogram occurring on average between 4 and 16 weeks after starting treatment.^{4, 5} Other alternatives to standard treatment with less evidence are doxycycline, ceftriaxone, tetracycline and azithromycin.^{4, 5, 11} The three cases reported in this series were treated with Benzathine Penicillin G and a few weeks after initiation, a significant improvement of the hepatogram was observed, with normalization between 10 and 36 weeks. Table 2 describes the main characteristics of the 3 cases described in this series. The rapid improvement in the alteration of the liver profile once the first dose of the treatment was administered would allow a diagnostic approach and thus subordinate the liver biopsy to those cases in which this improvement does not happen or there are other diagnostic hypotheses.

Table 2. Comparison of the main characteristics of the 3 clinical cases

	Sex	Age	ETS	Clinical manifestations	Pattern	Biopsy	Luetic serology	Status	Normalization (weeks)
1	M	43	No	Pruritus and choluria	Cholestatic	No	1/64 TPHA +	Secondary syphilis	28
2	M	52	No	Pruritus, asthenia, skin lesions	Mixed	No	1/256 THPA +	Secondary syphilis	10
3	M	39	HIV	Asymptomatic	Mixed	No	1/256 THPA +	Secondary syphilis	36

Hepatogram pattern (ALT/AP): greater than or equal to 5 (necrotic), mixed 2-5, less than and equal to 2 (cholestatic).

Conclusion

The increase in the incidence of syphilis, the morbidity and mortality associated with its chronicity, the simplicity of its diagnosis and the effectiveness of its treatment, are sufficient arguments to consider investigating it in patients with cholestatic/mixed hepatitis even in the absence of risk factors.

Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Malincarne L, Pasticci MB, Angeli G, Baldelli F, De Socio GV. Syphilis as a diagnosis of liver abnormalities in HIV. *Scand J Infect Dis* 2013; 45: 703-705.
2. Rinascente C, Candela G, Cervero M, Lobato A, Carbonell A. Acute non cholestatic hepatitis as the first manifestation of secondary syphilis. *Rev Gastroenterol Perú* 2015; 35: 247-249.
3. Rubio-Tapia A, Hujuel IA, Smyrk TC, Poterucha JJ. Emerging secondary syphilis presenting as syphilitic hepatitis. *Hepatology* 2017; 65: 2113-2115.
4. Mezzano G, Rondón F, Cid A, Parra F, Soto A, Gómez F. Hepatitis sífilítica: reporte de una serie de casos. *Rev Med Chile* 2019; 147: 251-255.
5. Ministerio de Salud del Uruguay. Recomendaciones de diagnóstico, tratamiento y vigilancia de las infecciones de transmisión sexual 2016: 1-92.
6. Pizarro R, Quezada M, Moreno F. Hepatitis sífilítica en paciente infectado con el virus de inmunodeficiencia humana. *Rev Chil Infect* 2001; 18: 143-146.
7. Aggarwal A, Sharma V, Vaiphei K, Duseja A, Chawla YK. An unusual cause of cholestatic hepatitis: syphilis. *Dig Dis Sci* 2013; 58: 3049-3051.
8. Tercero-Lozano M, Del Castillo-Codes I, Galvez-Fernández RM, Colmenero-Lechuga MM, Baeyens-Cabrera E. Hepatitis Sífilítica: una entidad poco frecuente. *RAPD ONLINE* 2013; 36: 131-133.

9. German MN, Matkowskyj KA, Hoffman RJ, Agarwal PD. A case of syphilitic hepatitis in an HIV-infected patient. *Hum Pathol* 2018; 79: 184-187.
10. Pizzarossa AC, Rebella M. Hepatitis in patients with syphilis: an overlooked association. *BMJ Case Rep* 2019; 12: 1-3.
11. Bork JT, Macharia T, Choi J, Gilliam BL, Buchwald UK. Syphilitic Hepatitis Treated With Doxycycline in an HIV-Infected Patient and review of the literature. *Sex transm Dis* 2014; 41: 507-510.
12. Ibáñez M, Varela M, Rodríguez-Peláez M, Mancebo A, García-Mayor MA, Pereira R. Luetic hepatitis. An emerging entity. *Gastroenterol Hepatol* 2009; 32: 610-613.
13. Affonso da Costa AB, Fornazari B, da Silva FPM, Frandoloso GA, Breda GL. Fulminant hepatitis in a patient with secondary syphilis. *Int J STD AIDS*. 2018; 29:1348-1350.
14. Lo JO, Harrison RA, Hunter AJ. Syphilitic hepatitis resulting in fulminant hepatic failure requiring liver transplantation. *J Infect* 2007; 54: 115-117.
15. Adachi E, Koibuchi T, Okame M, Sato H, Kikuchi T, Koga M. Liver dysfunction in patients with early syphilis: a retrospective study. *J Infect Chemother* 2013; 19: 180-182.
16. Manavi K, Dhasmana D, Cramb R. Prevalence of hepatitis in early syphilis among an HIV cohort. *Int J STD AIDS* 2012; 23: 4-6.
17. Suarez Iznaga R. Hepatitis Sifilítica. *Revista Cubana de Medicina* 2012; 51: 272-277.
18. De Miguel Gómez A, Benedicto Sánchez JR. Hepatitis sifilítica: una patología “poco frecuente”. *Medifam* 2002; 12: 108-109.
19. Ridruejo E, Mordoh A, Herrera F, Avagnina A, Mando OO. Severe Cholestatic Hepatitis as the First Symptom of Secondary Syphilis. *Dig Dis Sci* 2004; 49: 1401-1404.
20. Murphy CJ, Bhatt A, Chen W, Malli A, McGorisk T, Kelly SG. Syphilitic hepatitis. *Lancet Gastroenterol Hepatol* 2017; 2: 920.
21. Bronstein FN, Meyer B, Condat B, Loria A, Bronstein JA. Secondary syphilitic hepatitis in a fifteen-year-old boy. *Med Mal Infect* 2019; 49: 625-627.
22. Hussain N, Igbinedion SO, Diaz R, Alexander JS, Boktor M, Knowles K. Liver Cholestasis Secondary to Syphilis in an Immunocompetent Patient. *Case Reports Hepatol* 2018; 2018: 8645068.
23. Tolia S, Kassem H, Capatina-Rata A. The Great Impostor: transaminitis masking the coinfection of Syphilis and Human Immunodeficiency Virus. *Case Rep Med* 2017: 24819.
24. Huang J, Lin S, Wang M, Wan B, Zhu Y. Syphilitic hepatitis: a case report and review of the literature. *BMC Gastroenterol* 2019; 19: 191.
25. Horn CL, Jalali S, Abbott J, Stein MT. A Surprising Diagnosis: Syphilitic gastritis and hepatitis. *Am J Med* 2018; 131: 1178-1781.
26. Huang J, Lin S, Wan B, Zhu Y. A Systematic Literature Review of Syphilitic Hepatitis in Adults. *J Clin Transl Hepatol* 2018; 28: 306-309.