wjpmr, 2023, 9(6), 11-15

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

CLARIFICATION: ACTION TO TAKE IN THE FACE OF PRIMARY SCLEROSING CHOLANGITIS

L. Dehou*, A. Ibrahimi, M. ElAbkari and H. Abid

Hepato-gastroenterology Department, Sidi Mohammed Ben Abdellah University, Fez.

***Corresponding Author: L. Dehou**

Hepato-gastroenterology Department, Sidi Mohammed Ben Abdellah University, Fez.

Article Received on 15/04/2023 **Article Revised on 05/05/2023** **Article Accepted on 26/05/2023**

SUMMARY

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease with a highly variable course, characterized by inflammatory and fibrosing involvement of the intra and/or extra-hepatic bile ducts, of unknown mechanism, but probably dysimmune, often associated with inflammatory colitis. (MICI). The evolution is very variable but potentially serious. The two main risks are the formation of secondary biliary cirrhosis and the occurrence of cholangiocarcinoma, which is very difficult to diagnose early. In addition, in case of associated IBD, there is a high risk of colon cancer justifying special monitoring.

The diagnostic phase comprises several stages which are in fact parallel:
1) it is sclerosing cholangitis,
2) this cholangitis is not secondary,
3) what are the possible associated diseases?
And 4) how severe is PSC? Non-invasive methods occupy a major place in the diagnosis and follow-up of PSC. The diagnosis of PSC is essentially based on imaging of the bile ducts. Thus the fibro-inflammatory nature of the biliary involvement is much more often retained on the MRI appearance than proven histologically.

KEYWORDS: cholestasis, cholangio-MRI, cholangiocarcinoma.

l-INTRODUCTION

Primary sclerosing cholangitis is a chronic cholestatic disease with a very variable course, inflammatory and fibrotic involvement of the intrahepatic/and/or extrahepatic bile ducts, of unknown mechanism, probably dysimmune, often associated with IBD.[1,2] The diagnosis of primary sclerosing cholangitis is based on arguments: biological, radiological, histological and the association with inflammatory colitis. The main complications are: secondary biliary cirrhosis, cholangiocarcinoma, colorectal cancer.

The lack of knowledge of the pathogenesis of primary sclerosing cholangitis is a major obstacle to the development of a rational therapeutic proposal.

II-Epidemiology

-Primary sclerosing cholangitis is a disease of young subjects under 40 years of age affecting mainly men in 2/3 of cases.
-Disease that affects non-smokers, smokers having a lower risk of developing primary sclerosing cholangitis.
-It is a rare disease, of unknown prevalence, primary sclerosing cholangitis is less common than primary biliary cholangitis.
- Increased risk: cholangiocarcinoma, colorectal cancer.

III-Physiopathology: autoimmune, genetic, infectious and biliary hypotheses

➔Autoimmune
-Immune abnormalities (circulating immune complexes, AAN, AML, PANCA)
-Association with other autoimmune diseases (RCH, Crhon, gougerot syndrome)
➔ Genetics:
-First-degree relatives of patients with primary sclerosing cholangitis are at high risk of developing primary sclerosing cholangitis.
-The prevalence of Ag HLA B8, HLA D3 and HLADR W52a is higher in the general population
➔Infectious:
-Bacteria and viruses coming from the digestive tract via the portal vein could trigger an autoimmune mechanism causing primary sclerosing cholangitis (molecular

mimicry).
➔Biliary:
-The role of specific hepatobiliary transporters has been evoked at the origin of primary sclerosing cholangitis.

VI-Positive diagnosis: Table 1
1/Circumstance of discovery:
-The mode of revelation is extremely variable. Schematically the diagnosis must be evoked in three main circumstances.
➔"Biliary" symptomatology (cholangitis, jaundice, pain in the right hypochondrium or pruritus),
➔table of liver disease, very usually chronic and cholestatic (possibly reaching the stage of cirrhosis),
➔liver test abnormalities in asymptomatic patients (or with non-specific symptoms: asthenia, heaviness of the right hypochondrium)
-About 50% of patients have clinical symptoms[3]

2/The clinical examination:
-The examination may be normal
-We can find hepatomegaly, splenomegaly, subicterus, scratching lesions, melanoderma, xanthelesma
-Advanced forms: signs of hepatocellular insufficiency, signs of PH

3/Additional examinations:
➔Biology
a/ Liver assessment
- Cholestasis: there is an increase in alkaline phosphatase often more than 3N, an increase in GGT, bilirubin is normal at the beginning tends to increase gradually
-Cytolysis: transaminases can be normal or moderately elevated, a high rate (more than 5N) should raise suspicion of associated autoimmune hepatitis.
b/ Autoimmunity assessment:
-No specific markers
-Ab anti mitochondria are negative unlike PBC
- Anti-smooth muscle Ab + weakly positive anti-nuclear Ab (20-40%)
- Anti-cytoplasm+pANCA Abs are positive but of mediocre specificity.
c/HIV serology+assay of serum IGg4: to rule out secondary sclerosing cholangitis.

Tableau 1: Bilan inital de cholangite sclérosante primitive (Pr.Olivier CHAZOUILLÈRES).

Examen clinique, biologie	▪ Biologie standard et tests hépatiques usuels (bilirubine, phosphatases alcalines, transaminases, γGT, électrophorèse des protides, NFS plaquettes, TP, bilan lipidique, créatinine) ▪ IgG, IgM, IgG4, autoanticorps (pANCA, anti-noyaux, muscle lisse, microsome, mitochondries, transglutaminase,) ▪ ACE, CA 19-9, TSH, sérologie VIH
Imagerie : cholangio-IRM, idéalement 3D	
***Biopsie Hépatique :* non systématique**	Les indications formelles sont: ▪ suspicion de CSP des petits canaux biliaires (cholangio-IRM normale) ▪ augmentation importante des transaminases et/ou des IgG (association à hépatite auto-immune ?)
Endoscopie	▪ *Coloscopie* (avec biopsies systématiques) +++, si MICI non connue ▪ *Fibroscopie OGD* (si arguments pour une hypertension portale incluant plaquettes ≤ 150 000/µL et élastométrie ≥ 20 kPa)
Autres	▪ Élastométrie hépatique ▪ Ostéodensitométrie

➔ Imaging
a/ Abdominal ultrasound or abdominal CT scan:
-Thickening of the VBIH and extra-hepatic wall
-Sometimes moderate dilation of the VBIH
-Signs of PH
- normal: does not exclude the diagnosis of primary sclerosing cholangitis.
b/bili-MRI or cholangio-MRI[4.5]
- Cholangio-MRI can highlight stenoses that are usually multiple, alternating with usually moderate dilations, of the intra and/or extra-hepatic bile ducts (figure 1).

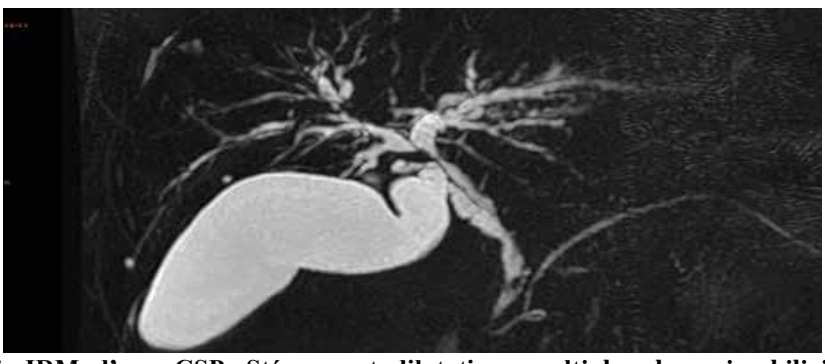

Figure 1: Cholangio-IRM d'une CSP. Sténoses et dilatations multiples des voies biliaires intra et extra-hépatiques.

➔ Remaining place of invasive examinations in the positive diagnosis of CSP.

a/Endoscopy: SPY GLASS

- ERCP no longer has a place for diagnostic purposes but remains indicated for therapeutic purposes or for carrying out endo-biliary samples in the event of suspected cholangiocarcinoma.[6]

-Colonoscopy with biopsies in search of IBD is systematically indicated when diagnosing PSC, even in the absence of digestive symptoms.

b/ Histology

- Liver biopsy is not essential for the diagnosis of PSC but remains indicated in case of suspicion of overlap syndrome or small duct PSC (Normal Bili MRI).[4, 5,7]

-Mixed form primary sclerosing cholangitis – autoimmune hepatitis (overlap)

VI-Extra-hepatic manifestation

➔ Bone disease (osteodensimetry and vitamin D assay)

PSC is associated with a risk of fractured osteoporosis. Bone densimetry should be performed at the time of diagnosis.[5] Vitamin D deficiency must be identified and corrected

➔ Chronic inflammatory bowel disease.

a/RCH

- UC associated with PSC have the following characteristics: it is usually pancolitis (exceeding the left angle in 90% of cases) that is not very active, or even completely quiescent.
- a colonoscopy with biopsies must be performed systematically in the assessment of a CSP.
- UC is diagnosed before PSC in more than 2/3 of cases but the reverse sequence is possible and UC can even begin after liver transplantation.
- no correlation between the severity of UC and the severity of PSC.

-Colectomy does not seem to modify the natural history of PSC (which can also begin after colectomy) but could reduce the risk of recurrence of PSC after liver transplantation

b/ Crohn's disease

- PSCs associated with CD seem to be more frequently of the "small bile duct PSC" type than in the case of association with UC and overall have a better prognosis.[8]

-An ileostomy should be avoided in patients with PSC because peristomal varices may develop, causing hemorrhages that are very difficult to treat.

-In patients with an ileo-anal anastomosis, the risk of pouchitis is increased in case of PSC.

-The risk of pouchitis persists after liver transplantation.[9]

c/CSP and colon neoplasia

-The European and American societies of hepatology (and endoscopy) as well as the ECCO group recommend colonic surveillance every year (ideally with chromo-endoscopy and directed biopsies) from the diagnosis of CSP in the event of known IBD.[6]

V-Severity Diagnosis

A permanent fear is the occurrence of cholangiocarcinoma (CC) which may be present from the diagnosis of CSP (30 to 50% of CC are diagnosed in the 1st year of knowledge of CSP), particularly in patients with severe biliary strictures.[10] The only clearly established risk factors are a higher age at diagnosis of PSC and a history of colon cancer.[11] A cholecystectomy is recommended for any gallbladder polyp > 8 mm due to a high risk of malignant transformation.[5]

VI-Complications

1- Cholangiocarcinoma

- This is the most serious complication of the disease
- The risk is greater if a greater seniority, associated IBD, if dysplasia or colon cancer.
- Early diagnosis is very difficult: a clinical or biological aggravation can occur apart from any cholangiocarcinoma, suggestive radiological abnormalities are inconstant.
- The screening strategy

*CA19-9/6months+ ACE

*Liver/gallbladder imaging every year

*In case of isolated or progressive stenosis Endo-biliary brushing with cytolgic examination or a bile sample looking for K-ras mutation and a PET-scan

-Surgical resection and transplantation are the only curative treatments for CC, paliatives: drainage with placement of a prosthesis.

2- Hepatocellular carcinoma.

3- Degeneration and colorectal cancer: The RCH-CSP association is a particular risk factor for the occurrence of adenocarcinoma of the colon.

4- Secondary biliary cirrhosis: at an advanced stage with its complications: HTP, IHC attention to the roles of drugs taken for IBD (Azathioprine, methotrexate)

5-Other: Recurrent cholangitis, complications of chronic cholestasis (steatorhoea, osteoporosis)

VII. CSP follow-up

-The monitoring of the CSP aims to

1) to identify patients with an unfavorable evolution in order to adapt treatment and follow-up methods.

2) early detection of hepatobiliary complications of the disease, in particular the occurrence of CC, cirrhosis or hepatocellular carcinoma.

3) to recognize and treat extra-hepatic complications, in particular colon cancer in case of associated. The elements of this monitoring are shown in (Table 2).

Table 2: CSP monitoring.

Tous les 6 mois	▪ Examen clinique ▪ Tests hépatiques simples et biologie usuelle
Tous les ans	▪ Imagerie du foie et des voies biliaires (échographie par opérateur expérimenté ou mieux IRM hépatique et biliaire) avec examen attentif de la vésicule biliaire (tout « polype » doit faire discuter une cholecystectomie dont l'indication est formelle si taille ≥ 8 mm) ▪ *coloscopie* avec biopsies (si MICI associée) dès le diagnostic de CSP (tous les 5 ans si absence initiale de MICI) ▪ Élastométrie hépatique ▪ Dosage sérique vitamine D
Tous les 2 à 4 ans	▪ Ostéodensimétrie

VIII. Processing

1/Medical Treatment

- Urso-deoxycholic acid at a dose of 15-20mg/Kg, very high doses of 28-30 mg/kg/day are contraindicated.

2/Other treatments can be combined in 2 situations.

- Single or clearly predominant tight stenosis at the level of the hilum or the common bile duct, symptomatic or with significant cholestasis: dilatation with a balloon and/or temporary biliary prosthesis by endoscopic route (CPR discussion)
- Presence of arguments in favor of associated autoimmune hepatitis (in particular, interface hepatitis with marked activity): corticosteroids (± azathioprine)

3/ Liver transplant

- Surgical treatment (apart from cholecystectomy) is now practically limited to liver transplantation for advanced forms.
- The 5-year survival rate of transplanted PSCs is greater than 70-80% in recent series (40).

Table 3: Eligibility criteria for liver transplantation during PSC.

Signes de décompensation de la cirrhose (ascite, encéphalopathie hépatique, hémorragie digestive par hypertension portale), (Child-Pugh B ou C)
Score MELD ≥ 15, ou Bilirubinémie totale ≥ 80 µmol/l pendant au moins 6 mois (en l'absence de possibilité de traitement endoscopique)
Indications particulières à la CSP : ▪ Angiocholites sévères à répétition (en l'absence de possibilité de traitement endoscopique). ▪ Cholangiocarcinome hilaire < 3 cm sans atteinte ganglionnaire et inclus dans un protocole très strict de radio-chimiothérapie pré-TH ▪ Prurit sévère et résistant (exceptionnel)

CONCLUSION

PSC remains a difficult disease to diagnose and treat. It is advisable to work in collaboration with the specialized centers of the FILFOIE sector (Sector of Rare Liver Diseases in adults and children, www.filfoie.com). For the practitioner, it is important to know the different clinical forms. A better understanding of the mechanisms involved is an essential objective. In the current state of knowledge, medical treatment remains based on UDCA but adjuvant treatment is clearly necessary and inclusion in therapeutic trials evaluating new agents should be encouraged.

ABBREVIATIONS

PSC: primary sclerosing cholangitis
RCH: Hemorrhagic recto-colitis
CD: Crohn's disease
CC: cholangiocarcinoma
UDCA: Ursodeoxycholic acid
TH: liver transplantation

REFERENCE

1. Lazaridis KN and LaRusso NF. Primary Sclerosing Cholangitis. N Engl J Med, 2016; 375: 1161-1170.
2. Dyson JK, Beuers U, Jones DEJ, Lohse AW and Hudson M. Primary sclerosing cholangitis. Lancet, 2018; 391: 2547-2559.
3. Lindor KD, Kowdley KV and Harrison ME, American College of G. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol, 2015; 110: 646-659; quiz 660.
4. European Association for the Study of the L. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol, 2009; 51: 237-267.
5. Lindor KD, Kowdley KV, and Harrison ME, American College of G. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol, 2015; 110: 646-659; quiz 660.
6. European Society of Gastrointestinal E, European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline. J Hepatol, 2017; 66: 1265-1281.
7. Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM et al. British Society of Gastroenterology and UK-PSC guidelines for the

diagnosis and management of primary sclerosing cholangitis. Gut, 2019.
8. Weismuller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H et al. Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associated With Course of Primary Sclerosing Cholangitis. Gastroenterology, 2017; 152: 1975-1984 e1978.
9. Singh S, Loftus EV Jr. and Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Am J Gastroenterol, 2013; 108: 1417-1425.
10. Chapman MH, Webster GJ, Bannoo S, Johnson GJ and Wittmann J. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. Eur J Gastroenterol Hepatol, 2012; 24: 1051-1058.
11. Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology, 2013; 58: 2045-2055.
12. European Association for the Study of the Liver. Electronic address eee. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol, 2016; 64: 433-485.