

Primary sclerosing cholangitis: a pre-malignant condition.

Abstract:

Primary Sclerosing Cholangitis (PSC), is a chronic, progressive cholestatic liver disease with no known cure. It is a serious disease and with this diagnosis comes an increased risk of developing cancer of the gallbladder, bile ducts or primary cancer of the liver known as hepatocellular cancer. PSC is associated with ulcerative colitis and patients with a dual diagnosis will have an increased risk of developing cancer of the bowel. In addition, patients can die from complications from colitis or liver failure and therefore, primary sclerosing cholangitis can be considered a pre-malignant condition. In view of this, one of the key aspects in managing PSC patients is regular surveillance to observe and rapidly treat any developing complications.

Primary sclerosing cholangitis (PSC) is a chronic, incurable cholestatic liver disease characterised by inflammation and fibrosis, leading to irregular and patchy stricturing of the intra and extrahepatic bile ducts (Chapman 2015; Lee and Kaplan, 1995). The disease progresses slowly over 10 - 15 years and will lead to cirrhosis in most patients, with the associated complications of portal hypertension, liver failure and premature death (Yimam and Bowlus 2014; Lee and Kaplan, 1995).

In a normal liver, bile is made from the breakdown of the haem part of haemoglobin. Once made, bile is carried through the biliary tree into the small intestine. Bile contains bile acids which is crucial for the digestion and absorption of fats that contain soluble vitamins: A, D, E and K. Disorders that impair the production of bile result in the condition known as cholestasis. There are many possible causes of cholestasis with PSC being one of them.

Aetiology

The cause of PSC is unknown but it is linked with inflammatory bowel disease, in particular, ulcerative colitis (UC), suggesting an autoimmune component to this disease (Broome and Bergquist, 2006; Bambha et al, 2003). It affects more males than females with a ratio of 2:1 (Nayagam et al, 2016). Most patients present with the condition between the age of 25 – 40 years; with a mean age of 40, but it can affect children (Chapman et al, 2010; EASL, 2009). According to Chapman, (2015) 75% of patients with PSC have UC and approximately 3-10%

of patients with a diagnosis of UC will develop PSC. Although associated as potentially an autoimmune condition a further theory is that PSC, with a dual diagnosis of UC, may be related with “leaky gut” in which the inflammatory component of UC increases disruption of bowel mucosa. This in turn leads to increased permeability through the bowel wall, leading to bacterial translocation into the portal venous system (Adams et al 2008). Studies by Grant et al (2002, 2001), suggested that the circulation of lymphocytes, which originated from the intestine, may cause inflammation of the liver although there is no confirmed link to PSC at present.

Diagnosis

A diagnosis of PSC is made in patients with increased blood levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT); a hallmark of PSC. In 95% of cases, these liver function test (LFT) readings can be between 3 to 10 times the upper limit of normal (Yiman and Bowlus, 2014). If there is no other explanation for the raised LFT’s, then magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) is undertaken. If these tests reveal bile duct changes with multifocal strictures and dilation of segments of the bile duct, then PSC can be diagnosed, when other cholestatic disorders have been excluded. Throughout the disease course, it is acknowledged that the LFT’s can fluctuate and sometimes normalise but this will vary in individual patients and over time (Mendes et al, 2006).

Many patients with PSC are initially asymptomatic and the diagnosis is made incidentally when liver function tests are checked and abnormal findings such as a raised ALP and GGT is discovered and investigated, especially in patients with pre-existing UC. It is important that nurses working within gastroenterology units; monitoring patients with UC are aware of the clinical significance of a raised ALP and GGT to either; organise further investigations and alert the appropriate medical team of the raised blood result.

Symptoms of PSC

Other clinical symptoms of PSC commonly include fatigue and frequently attributed by patients to busy lifestyles such as work and looking after young children. This symptom can often be ignored for many months or even years and it is not until other signs and symptoms are apparent such as: right upper quadrant abdominal discomfort, pruritis,

weight loss, and temperature with rigors, suggestive of inflammation of the bile ducts, that patients seek medical or nurse advice. Jaundice can be another symptom of PSC but is uncommon unless cholangiocarcinoma; a bile duct cancer, or bile duct stones are present. Suspicion would be roused of a possible cholangiocarcinoma or hepatocellular carcinoma with a sudden or further deterioration in liver function tests (LFT's) and jaundice; with either of these symptoms further investigations should be undertaken to rule out carcinoma.

Unfortunately, there is no cure for PSC and no drug treatments with proven mortality benefits (Nayagam et al, 2016). Evidence suggests that in symptomatic patients, from the time of diagnosis to death, or liver transplantation is 12-15 years (Yiman and Bowlus, 2014). Studies also acknowledge that patients who are symptomatic at diagnosis have a shorter median survival than those who are asymptomatic (Chapman, 2015).

Small duct PSC

There are variant forms of PSC, such as small duct PSC and this can account for up to 16% of the PSC population. Small duct PSC affects the very small bile ducts so makes it difficult to distinguish on ERCP or MRCP as both tests can look normal. Therefore, the diagnosis of small duct PSC (SDPSC) is made from histology from a liver biopsy and biochemically from the blood tests (Bjornsson et al, 2008). Evidence suggests that SDPSC has a slower disease progression compared to large duct PSC. Because of this, there is a decreased risk of cholangiocarcinoma, with an increased survival rate compared to large duct PSC. However, 12% of SDPSC will go on to develop large duct disease (Bjornsson et al, 2008; Angulo et al, 2002).

Cholangitis

PSC causes multifocal stricturing of the bile ducts which in turn can disrupt the production and flow of bile. This can lead to the development of cholestasis and cholangitis. Cholangitis is an infection of the bile ducts, which has a high morbidity and mortality and this increases with the age of the patient (Kumar and Clark, 2012). According to Chapman, (2015) attacks of cholangitis in PSC patients are uncommon and tend to occur after surgical instrumentation such as endoscopic retrograde cholangiopancreatography (ERCP).

Consideration should also be given to patients with suspected or known PSC who undergo a

liver biopsy. These patients may require prophylactic antibiotics to be administered to prevent cholangitis.

Drug treatment

Ursodeoxycholic acid (UDCA) is often prescribed by clinicians as it can improve ALP levels when prescribed at a dose of 13-15mg/kg. Nevertheless, there is no conclusive proof that it alters disease progression even if ALP levels fall (Lindor, 1997); although there is some evidence to suggest it has a protective mechanism in the development of bowel cancer (Pardi, et al, 2003). A meta-analysis on the use of ursodeoxycholic acid in PSC found that at the standard or a higher dose presented no real difference in the risk of developing a cholangiocarcinoma or decreased mortality (Triantos et al, 2011). Published Guidelines by the American Association for the Study of the Liver (AASLD; Chapman et al, 2010) advocate not using ursodeoxycholic acid for the treatment of PSC. The European Association for the study of the Liver (EASL, 2009) made no recommendations for its use in the treatment of PSC due to the limited available research.

Cholangiocarcinoma

Approximately 37% of PSC patients will die from liver failure due to cirrhosis and a further 10 - 30% may develop cholangiocarcinoma. The risk of developing a cholangiocarcinoma increases with the length of time diagnosed with PSC (Claessen et al, 2009). 50% of cholangiocarcinoma's are diagnosed within the first year of PSC diagnosis (EASL, 2009). Unfortunately, survival after diagnosis of a cholangiocarcinoma is poor even if surgery is performed; with less than a 20% survival rate after 3 years (Rosen and Nagorney, 1991). Distinguishing between benign strictures of the bile duct or a cholangiocarcinoma can be difficult and by the time cholangiocarcinoma is diagnosed it may already be at an advanced stage; with deranged LFT's, where palliative chemotherapy, surgical resection or transplant is no longer an option.

A study by (Bergquist, et al., 2002) found that over 13% of a 600 cohort of PSC patients developed either a cholangiocarcinoma, hepatocellular carcinoma or gallbladder cancer. This equates to a risk of 161 times greater than the general population. Patients with a dual diagnosis of PSC and UC may develop complications from colitis or develop colonic cancer, both of which can lead to patient death. Therefore, PSC can be classed as a pre-malignant

condition (Chapman, 2015). For this reason, nurses caring for patients with this illness require an understanding of the disease process to appreciate the seriousness of the condition and its associated complications, enabling early detection and rapid instigation of medical or surgical treatments.

Bowel Cancer and surveillance

PSC patients with a dual diagnosis of UC are at risk of developing bowel cancer. According to a seminal study by Shetty et al., (1999) 76% of bowel cancers were found on the right side of the colon in patients with the dual diagnosis. This and other evidence regarding the increased risk colorectal cancer development has led to PSC guidance being produced by AASLD (Chapman et al, 2010) which recommends a full colonoscopy with biopsies for all newly diagnosed patients as well as 1-2 yearly surveillance colonoscopies thereafter.

Gallbladder cancer and surveillance

PSC patients have an increased risk of developing gallbladder cancer especially if gallbladder polyps are present (Said et al., 2008; Lewis et al., 2007; Buckles et al., 2002). Both the AASLD and European Association for the Study of the Liver (EASL) guidelines recommend annual gallbladder surveillance in the form of an abdominal ultrasound (Chapman et al, 2010; EASL, 2009). Cholecystectomy is recommended if any gallbladder polyps are detected, regardless of the size. PSC patients who have undergone a cholecystectomy will no longer require the annual gallbladder surveillance

Hepatocellular Cancer

Cirrhosis of the liver can lead to the development of hepatocellular cancer (HCC). However, the risk of developing a HCC is dependent on the underlying cause of the liver disease. In a retrospective analysis of 119 PSC cirrhotic patients, no cases of HCC were identified (Zenouzi et al., 2014) Currently, there is no recommendation for screening in PSC cirrhotic patients. Although this may be the case, it can be easier for nurses, who are often tasked with the job of surveillance monitoring, to organize 6 monthly surveillance ultrasound scans on all cirrhotic patients, rather than singling out specific cohorts. This is especially pertinent since NICE (2017) have released the Liver Disease quality standard (QS152) that, “adults with

cirrhosis are offered 6-monthly surveillance for hepatocellular carcinoma”, although it is acknowledged that this was not inclusive of autoimmune disease.

Fat soluble vitamin deficiencies

As PSC progresses, patients can develop deficiencies in fat-soluble vitamins such as A, D E and K, due to the disruption in the production and flow of bile. This can cause further complications associated with vitamin deficiencies. All patients diagnosed with PSC should be offered a dual energy X-ray absorptiometry scan (DEXA scan). This is a special type of X-ray that measures bone mineral density (BMD) to diagnose osteopenia or osteoporosis; a complication of inadequate Vitamin D intake. DEXA scans should be repeated every 2-5 years depending on the initial result. If osteopenia is diagnosed on the initial DEXA scan then Adcal-D3, 2 tablets, once daily should be prescribed as a prophylactic measure against the development of osteoporosis. Adcal-D3 contains vitamin D and calcium and should not be prescribed in patients with a known history of renal stones as this can exacerbate stone formation. If osteoporosis is diagnosed, then bisphosphonates are prescribed. If the patient is unable to tolerate oral tablets or has known varices, then bisphosphonates should be administered intravenously. This is recommended as oral bisphosphonates are known to cause mucosal irritation of the gastro intestinal (GI) tract causing nausea, vomiting, epigastric pain and dyspepsia (De Groen et al., 1996) thereby increasing the risk of GI haemorrhage.

Administration of bisphosphonates

There are strict instructions for the correct oral administration of bisphosphonates to reduce the risk of GI complications. These instructions have been issued by Medicines and Healthcare Products Regulatory Agency (MHRA, 2014) and are also found within leaflets issued with the medication. It is of utmost importance that patients are advised on how to correctly take these medications to avoid serious side effects. ~~Health care professionals~~ Nurses monitoring, or looking after patients on gastro/hepatology wards should be aware of the correct route of administration of bisphosphonates and can advise accordingly; reiterating the fact that no other food or medicines should be taken for an hour after ingestion of bisphosphonates. This is especially pertinent to prescribers, with regards to the timing of medications for inpatients.

Monitoring for vitamin deficiencies

In view of potential vitamin deficiencies, further monitoring of the other fat soluble vitamin levels such as Vitamin A, E and K should be undertaken at least annually and supplementation prescribed if required. Clotting disorders due to a deteriorating liver function or a deficiency in vitamin K, especially if jaundice is present, should also be considered and monitored closely. If clotting is normal, then a clotting screen should be checked at least yearly and introduced more frequently if abnormalities are detected.

Immunoglobulin G4 related sclerosing cholangitis

A separate entity called, Immunoglobulin G4 (IgG4) related sclerosing cholangitis can closely mimic PSC but unlike PSC can be treated with steroids and is reversible (Zen, et al, 2004). Therefore, correct diagnosis is important for the correct therapeutic treatment. IgG4 is a multisystem disorder which can affect pancreas, salivary glands, aorta, thyroid, kidneys, lungs and the liver. IgG4 levels can be raised in PSC but are seen at higher levels in IgG4 sclerosing cholangitis. Therefore, IgG4 levels should be checked to help differentiate between the two conditions. The diagnosis of IgG4 disease can be made by taking a good history; being alert to other symptoms suggestive of a multi system involvement and checking IgG4 level.

Transplantation

In patients in the advanced stages of PSC, a liver transplant is the only treatment option. Liver transplant is also offered to patients with intractable pruritis or recurrent cholangitis. Unfortunately, PSC can reoccur in the transplanted liver with studies showing between a 10-30% recurrence rate within 5 years (Chapman, 2015; Charatcharenwitthaya and Lindor, 2008). Post-transplant, there is a five year survival rate of around 75-80%. In patients with a dual diagnosis of UC it is recognised that the UC may deteriorate and that a further 5-10% may develop colorectal cancer (Charatcharenwitthaya and Lindor, 2008). Annual colonoscopy surveillance should continue post-transplant.

Summary of diagnosis and treatment

	AASLD Recommendations (Chapman et al., 2009)	EASL Recommendations (EASL, 2009)
Diagnosis	Raised ALP and GGT when ERCP and MRCP show bile duct changes of multifocal strictures and dilatations (beading)	“
Patients with normal ERCP/MRCP but raised ALP/GGT	Liver biopsy to exclude SDPSC or autoimmune hepatitis overlap	“
Exclude IgG4 disease	Measure IgG λ levels	“
Autoantibodies	No role for diagnosing PSC	“
Bone scan	On diagnosis Then 2-3 yearly	No specific recommendation
osteopenia	Calcium 1-1.5g and Vitamin D 1000iu daily	No specific recommendation
osteoporosis	Biphosphonate and calcium and vitamin D supplements	No specific recommendation
Osteoporosis and varices	Parenteral preparation rather than oral	No specific recommendation
New diagnosis PSC no History IBD	Full colonoscopy	Full colonoscopy
IBD and PSC	Full colonoscopy 1-2 yearly intervals	Annual colonoscopy
USS	Annual – surveillance mass lesions of gallbladder. If found - cholecystectomy	Annual – surveillance mass lesions of gallbladder. If found – cholecystectomy
CCA	If no cirrhosis – surgical resection or transplant	
UDCA	Recommend against the use	Although improves LFT’s no benefit on survival. No recommendation for general use of UDCA
UDCA for chemoprevention of colorectal cancer	Recommend against the use	Limited evidence but may be considered in those with a strong family history, previous colorectal cancer or longstanding extensive colitis
Immunosuppressants and steroids	Recommend the use in autoimmune hepatitis overlap	Role in PSC AIH overlap None can be recommended for PSC alone
Pruritis	Antihistamines	No specific recommendation

	Cholestyramine 4g up 16 g daily Rifampicin 150mg -300mg (BD) Opiate antagonist (Naltrexone) 50mg daily Sertraline 75-100mg daily	
Liver transplant	Advanced liver disease	Late stage PSC Recurrent bacterial cholangitis Cholangiocyte dysplasia

Summary of surveillance

- All PSC patients should have regular surveillance in the form of:
- Oesophago-gastro-duodenoscopy (OGD) for varices surveillance if cirrhotic
- 6 monthly ultrasound scans of the liver if cirrhotic for hepatocellular carcinoma
- Any sudden deterioration in LFT's - surveillance ultrasound scan of the liver for cholangiocarcinoma or hepatocellular carcinoma.
- Annual ultrasound scan for the development of gallbladder cancers
- Annual colonoscopies for bowel cancer surveillance
- Annual blood test monitoring for vitamin deficiencies and increased in frequency if abnormalities detected
- DEXA scan on diagnosis of PSC then 2-5 yearly for the surveillance of osteopenia or osteoporosis.

Conclusion

PSC is a serious disease, with many associated complications and as such, can be considered a premalignant condition. It is important for all health professionals; especially those who look after PSC patients on the wards, or on an outpatient basis, are aware of the signs and symptoms of disease progression and complications associated with PSC. With this knowledge, it will enable health care professionals to offer the patient correct advice,

assistance, timely surveillance and support when needed as well as expediting treatment and/or investigations when required in a judicious manner.

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