CLINICAL REVIEW

Primary sclerosing cholangitis

LAURENCE TINCKLER
M.D., Ch.M., F.R.C.S., F.A.C.S.

Formerly Professor of Surgery, University of Singapore

Summary

The literature on the subject of sclerosing cholangitis is reviewed.

The value of conserving the gall bladder, of operative cholangiography and of the administration of steroids in the management of these patients is emphasized.

PRIMARY sclerosing cholangitis, stenosing cholangitis, fibrosing cholangitis, chronic obliterative cholangitis are all terms referring to a rare diffuse type of chronic inflammation of the entire common bile duct and at times of the hepatic ducts and their radicles. In most instances, sclerosing cholangitis is idiopathic or primary.

Bartholomew *et al.*, in 1963 found only twenty unequivocal cases reported in the previous 40 years and considered that the rarity of the syndrome and the poor results of treatment warranted reporting of individual cases, particularly if they provided new aetiological or therapeutic data. Although Schwartz & Dale (1958) described a diffuse obliterative ductal sclerosis in patients with gall-stone disease, stenosing cholangitis involving only a short segment of the common duct may occur and Baddeley & Stammers (1964) infer that such lesions may diffusely spread throughout the bile duct system.

Glen & Witsell (1966) stipulate the following criteria for making the diagnosis: progressive biliary obstruction, exclusion of surgical injury as a possible causative agent, operative demonstration of a diffuse sclerosing process involving the common duct, frequently the hepatic ducts and sometimes the gall bladder, a fibrotic process and absence of malignant neoplasm requiring histological confirmation.

Incidence

The first case was reported by Delbet in 1924; and the second 1 year later by Lafucade (1925). Judd reported three patients in 1926 all of whom,

however, had had previous biliary surgery. Miller reported a case in 1927.

Carter & Gillette in 1951 described fifteen patients with strictures involving the intrahepatic biliary system. In 1963, Bartholomew *et al.* reported two patients and suggested an association with retroperitoneal fibrosis and Riedel's thyroiditis. They considered the possibility that a hypersensitivity reaction might be the underlying aetiological factor. In one of their patients, as well as in the experience of Schwartz & Dale (1958) corticosteroids appeared to be of definite therapeutic value.

In 1958, Schwartz & Dale found only thirteen authentic cases of the primary type in the literature and added six cases of their own. The majority of cases reported were examples of extensive involvement of the entire common bile duct with, at times, cystic duct involvement. They suggested that the disease is commoner than previously considered and therefore its recognition and therapy assume greater significance; they noted that matters of aetiology, clinical course and final prognosis remain speculative at this stage. Involvement of the intrahepatic ducts as in the case described by Klemperer (1937) and by Shumarer (1958) is evidently exceedingly rare.

The disease is one of adult life, commonly in patients of middle-age, and men are affected more often than women.

Manesie & Sullivan (1965) reviewed the literature between 1924 and 1964 and found only twenty cases fulfilling the criteria. Wolubitsky & Mackenzie (1964) found on review of the literature between 1924 and 1964, twenty-four acceptable cases out of 100 reported and added four of their own.

Warren, Athanassiades & Monge (1966) found the records of forty-two patients at the Lahey Clinic and noted that twelve of these patients had associated ulcerative colitis; eleven patients had no history of gall stones or previous surgery, and there were no other associated diseases; a fourth group included four patients in whom severe periportal inflammation preceded the sclerosing obliterative process. In one of these four patients suppuration also had occurred.

Glen & Witsell (1966) reported seven patients under their care at the New York Hospital. Operative findings were similar in all patients. The gall bladder in each patient exhibited some degree of fibrosis but calculi were present in only three. Enlargement of lymph nodes along the common duct was frequently accompanied by oedema and fibrosis in the region of Calot's triangle. The external diameter of the common duct although not increased and even sometimes reduced was firm and thickened to palpation in every patient. Narrowing of various portions of the biliary tree was demonstrated by operative cholangiography in six of the seven patients. Radiological visualization of the biliary system could not be accomplished in the remaining patient because almost complete obliteration of the lumen of the common duct made introduction of the contrast agent impossible. Common duct exploration was accomplished in five patients and in each was demonstrated either localized segmental or general diffuse involvement of the ductal system. When the lumen was narrowed there was a corresponding increase in the thickness of the wall. The process was so marked in one patient that common duct exploration was not feasible. Biopsy of the common duct was performed on four patients; dense vascular fibrous tissue was demonstrated in three of the biopsies, while the fourth showed only common duct mucosa.

Clinical picture

The usual clinical picture is one of slowly progressive jaundice often associated with discomfort in the abdomen or upper lumbar region. True biliary colic is unusual. The age range has been from 21–67 years, patients in the fourth and fifth decade being more common. The ratio of males to females has been about 3:1. Laboratory findings have invariably been those of obstructive jaundice. Symptoms of sclerosing cholangitis are indistinguishable from those associated with chronic gall-bladder disease, the most frequent sign being a slowly deepening jaundice over a period of weeks or months. Hepatomegaly is not usual. A definitive diagnosis is established by abdominal exploration, by X-ray and by histological study of the biliary tree.

The disease results in chronic biliary obstruction followed by secondary biliary sclerosis, eventual liver failure and terminal coma. Less often portal hypertension and bleeding oesophageal varices occur as terminal events. It is associated in a significant number of cases with chronic, moderately severe ulcerative colitis, often with stones, occasionally with Riedel's struma and peri-ureteric fibrosis. It should not be confused with acute obstructive suppurative cholangitis and should be differentiated from cholangiocarcinoma which simulates primary

sclerosing cholangitis clinically and in gross appearance.

Pathology

Great thickening of the wall of the involved duct or ducts associated with marked luminal narrowing characterizes the lesion. In most cases the common duct lumen has been between 3 and 5 mm in diameter (Jackson & MacVey, 1962), it being possible to insert a fine probe only into the lumen. The wall of the ducts may be up to eight times the normal thickness (Roberts, 1955) and on palpation the common duct is cord-like throughout. Lymph nodes about the duct are usually enlarged and at times the entire area is encased in dense adhesions (Schwartz & Dale, 1958). The duct mucosa is normal, the duct thickening involving the sub-mucosa and sub-serosa in a diffuse fibrotic process with oedema intervening. Biopsy of the liver shows bile stasis and periportal fibrosis. The diagnosis is made on the basis of findings at operation which may be of a dense inflammatory reaction in the region of the gall bladder and gastro-hepatic ligament. This may be so intense that demonstration of the common duct is difficult; its size is not diagnostic because this represents the sum of the narrowed lumen and thickened wall (Schwartz & Dale, 1958). Palpation of the common duct imparts the sensation of a cord-like structure which may feel like a thrombosed blood vessel. When the wall of the common duct is incised the diagnosis should be clear; the wall is obviously thickened, cuts with difficulty and the edges of the incision pout outwards. It is possible to insert a fine probe only into the lumen.

It is of interest that in all cases in which operative cholangiograms were obtained, radio-opaque material was seen to enter the duodenum thus indicating that obstruction is not always complete.

Bartholomew *et al* (1963) say that essentially there is inflammatory fibrosis quite comparable to, if not identical with that seen in Riedel's struma. The histological similarity of Riedel's struma and idiopathic fibrous mediastinitis has been emphasized, and it seems logical to infer that Riedel's struma, idiopathic fibrous mediastinitis, sclerosing cholangitis and retroperitoneal fibrosis represent a basically similar pathological process occurring in different sites.

According to Glen & Witsell (1966) the operative findings seem to vary with stages of the disease but the characteristic changes are located in the gall bladder and especially in the common duct. Although the gall bladder is frequently calculus free, stones are occasionally found. The wall of the gall bladder is thickened and fibrotic, less markedly in the region of the ampulla and cystic duct. Similar and usually more pronounced changes are present

in the common duct. Instead of the soft, pliable, easily compressible structures which one normally finds, the common duct in patients with this condition is firm and rigid and rolls between the examining fingers like a pencil. Opening the common duct confirms the fact that the lumen has been reduced to a point which frequently will hardly admit the smallest probe. This process may be localized or may involve the entire common duct and major portions of the intrahepatic biliary system. The use of operative cholangiography is valuable in determining the extent of the disease process. Histological study of sections of the wall of the common duct and hepatic ducts both by frozen sections at the time of operation and by permanent sections later is important, as it has been pointed out by Thorbjarnarson (1958) and Altmeir *et al.* (1957) that carcinoma of the biliary tract can be a slow-growing lesion which produces symptoms clinically indistinguishable from those of chronic sclerosing cholangitis. Gross findings at operation are not diagnostic and interpretation of frozen sections from this area is notoriously difficult. In spite of every effort, carcinoma may not be recognized until permanent sections are available, and occasionally the correct diagnosis is not made until necropsy.

Although the occasional patient may experience an apparent remission of the disease and enjoy a long asymptomatic interval, the long-term prognosis for most patients is dismal, the usual clinical course being gradual progressive biliary obstruction, deepening jaundice, physical wasting and finally death from biliary cirrhosis.

Aetiology

In most instances, sclerosing cholangitis is idiopathic or primary although some reporters have described diffuse obliterative ductal sclerosis in patients with gall-stone disease (Schwartz & Dale, 1958) the cause is essentially unknown.

Ransom & Malcolm (1934) mentioned that an occasional patient with congenital stricturing of the bile ducts might survive to adult life, but support for this is lacking. According to Ralston, syphilis might give rise to a congenital stricture of the common bile duct.

Biliary tract lithiasis, chronic sclerosing pancreatitis and duct injury cannot be incriminated as causes. Viral infection has been considered but no proof has been forthcoming. The involvement is not primarily mucosal so that chemical injury from bile or pancreatic juice seems unlikely. Bacterial infection has been dismissed as a primary factor by most observers. Any infective agent occurring in association with the disease would probably be carried by the periductal lymphatics.

A hypersensitivity response has been postulated by Schwartz & Dale (1958) since cortisone appears to have a strikingly favourable therapeutic effect. Cole (1958) has mentioned the possibility of the existence of a Schwartzman type reaction; Goldgrabber & Kirsner (1960) have reported a case of ulcerative colitis with granulomatous cholecystitis and fibrosing choledochitis and discussed the possibility that a hypersensitivity reaction accounts for these wide-spread tissue changes.

Because, in the two cases reported by Bartholomew *et al.* (1963), there was eosinophilia with associated fibrosing retroperitonitis (which is known to be frequently accompanied by eosinophilia) they also considered the role of an allergic or hypersensitivity reaction and diffuse disturbance of collagen tissue in the pathogenesis of sclerosing cholangitis.

In the series of patients reported by Warren *et al.* (1966) the disease existed by itself or in association with another disease such as ulcerative colitis, biliary calculus disease or severe inflammation around the porta hepatis. No proof exists to date for a causal relation between primary sclerosing cholangitis and other associated diseases. However, the presence of ulcerative colitis in twelve patients in the series, makes it possible that a causal relation exists between the two conditions, and supports the view that low-grade bacterial infection, with the large bowel as the source, reaching the biliary tract through the portal circulation might be responsible for chronic inflammation of the biliary tract and consequent fibrosis and obliteration of the ducts. In support of this view, they quoted studies by Denien (1964), Brooks & Slaney (1958) and Schatten, Ouprez & Holden (1955) concerned with the passage of bacteria from the large bowel to the biliary tract. According to Popper & Szanto (1956) intrahepatic damage associated with ulcerative colitis resulting in cholestasis, pericholangitis and periductal fibrosis develops as a result of bacterial infection, and raises the possibility that the intrahepatic lesions in ulcerative colitis constitute a different disease from primary sclerosing cholangitis or that the two may be simply stages of the same process.

Gravane, Bogetti & Iovine (1958) have suggested that chronic sclerotic cholecystitis and chronic relapsing pancreatitis may be manifestations of a localized collagen disease for which a course of steroid therapy would be justified.

Although low-grade bacterial infection has been considered, there has been no consistent demonstration or identification of an organism.

Rolleston & Hayne (1901) and Mathew (1924) have suggested that some of the cases represented the later results of congenital biliary stenosis due to ascending cholangitis during the intra-uterine state;

however the appearance of manifestations of the disease in middle and late years of life rules against this concept.

Primary hepatic disease cannot be implicated as an aetiological factor as biopsy of the liver in these cases shows that the liver is involved secondarily with an obstructive biliary cirrhosis. Laboratory tests of liver function do not always demonstrate hepato-cellular dysfunction and when abnormal they have returned to normal rapidly after the biliary obstruction has been relieved.

The possibility that an auto-immune process may be operating exists, and the occasional apparent favourable response of this condition to corticosteroids is consistent with auto-immunity being an aetiological factor.

Treatment

As the cause of chronic sclerosing cholangitis remains unknown, treatment is of necessity empirical. Operation is necessary to establish the diagnosis by surgical exploration; biliary calculi when found must be removed but the gall bladder should be left intact as it may be invaluable later for biliary diverting procedures. Should it be possible to insert a T-tube into the common bile duct, this should be done to decompress the biliary tract but in most cases the lumen of the common bile duct will not permit intubation. Where communication of the bile-duct system permits, decompression of the biliary tract can be affected by cholecystostomy for prolonged drainage. Operative cholangiography at the time of surgical exploration is advisable in order to confirm the suspected diagnosis.

Drugs such as dehydrocholic acid (Decolen) 250 mg three times daily, can be used to increase the fluidity of the bile and therefore facilitate flow. A broad spectrum antibiotic such as tetracycline which achieves high levels in the bile may be added to the postoperative treatment to protect against secondary bacterial cholangitis. The administration of corticosteroids is indicated, the drugs acting in two ways; firstly as anti-inflammatory agents having a direct action on the disease process leading to decrease in the thickness of the walls of the bile ducts and an increase in the lumen; secondly, decreasing the bilirubinaemia by a direct action. Administration of cortisone 100–300 mg daily is initiated promptly in the postoperative period changing to prednisone 40–50 mg daily for long-term use.

Corticosteroid treatment should be continued for several months and re-introduced should recurrence of symptoms and/or jaundice take place. Sodium dehydrocholate may be given intravenously for several days to increase the fluidity of the bile and later by mouth in tablets of 0.25 g and one or two tablets after meals.

With decompression of the biliary tract combined with steroid therapy the prognosis of primary sclerosing cholangitis has improved strikingly in recent years, Schwartz & Dale (1958) for instance, reporting only one fatality among their six patients.

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References

- ALTEMEIER, W.A., GALL, E.A., ZINNINGER, N.N. & NOX-WORTH, P.I. (1957) Sclerosing carcinoma of the major intra-hepatic bile duct. *Archives of Surgery*, **75**, 450.
- BADDELEY, R.M. & STAMMERS, F.A.R. (1964) Benign, non-traumatic stricture of the extra-hepatic bile duct. *British Journal of Surgery*, **59**, 25.
- BARTHOLOMEW, L.G., CAIN, J.C., WOOLNER, L.B., UTZ, D.C. & RERRIS, D.O. (1963) Sclerosing cholangitis; its possible association with Riedel's stroma and fibrous retroperitonitis; report of two cases. *New England Journal of Medicine*, **269**, 8.
- CARTER, R.F. & GILLETTE, L. (1918) Benign stricture of the intra-hepatic biliary ducts. *Surgery, Gynecology and Obstetrics*, **26**, 81.
- COLE, W.H. (1958) Discussion of paper of Schwartz & Dale.
- DELBET, P. (1924) Retrecissement du choledoque: cholecysto-duodenostomie. *Bulletin et mémoires de la Société de Médecine de Paris*, **50**, 1144.
- GLENN, F. & WHITSELL, J.C. (1966) Primary sclerosing cholangitis. *Surgery Gynecology and Obstetrics*, **123**, 1037.
- GOLDGRABER, M.B. & KIRSNER, J.B. (1960) Chronic granulomatous cholecystitis and chronic ulcerative colitis. *Gastroenterology*, **38**, 821.
- GRAVANO, L., BOGETTI, H. & IOVINE, J.R. (1958) Colangitis cronica estenosante, pancreatitis cronica recidivante: expression de una colangenosis localizada. *Prensa medica argentina*, **45**, 1613.
- HOLUBITSKY, M.D. & MCKENZIE, A.D. (1964) Primary sclerosing cholangitis and of the extrahepatic bile ducts. *Canadian Journal of Surgery*, **7**, 277.
- JUDD, E.S. (1926) Stricture of the common bile duct. *Annals of Surgery*, **84**, 404.
- KLEMPERER, P. (1937) Chronic intrahepatic obliterating cholangiolis. *Journal of the Mount Sinai Hospital*, **4**, 279.
- LAFOURCADE, J. (1925) Deux observations D'obliteration cicatricielle de choledoque. *Bulletin et mémoires de la Société de Médecine de Paris*, **50**, 828.
- MANESIS, J.G. & SULLIVAN, J.F. (1965) Primary sclerosing cholangitis. *Archives of Internal Medicine*, **115**, 137.
- POPPER, H. & SZANTO, P.B. (1956) Intrahepatic cholestasis (cholangiolitis). *Gastroenterology*, **31**, 683.
- ROBERTS, J.M. (1955) Stenosing cholangitis. *Western Journal of Surgery*, **63**, 253.
- ROLLESTON, H.D. & HAYNE, L.B. (1901) The care of congenital hepatic cirrhosis with obliterative cholangitis. *British Medical Journal*, **1**, 758.
- ROLLESTON, H. & MCNEE, J.W. (1929) *Disease of Liver, Gall-bladder and Bile Ducts*. Macmillan, London.

- RANSOM, H.K. & MALCOLM, K.D. (1934) Obstructive jaundice due to diffuse contracture of extra-hepatic bile ducts. *Archives of Surgery*, **28**, 713.
- SCHWARTZ, S.I. & DALE, W.A. (1958) Primary sclerosing cholangitis: review and report of six cases. *Archives of Surgery*, **77**, 439.
- HUMARER, W.B. (1958) Discussion of paper of Schwartz & Dale.
- SCHATTEN, W.E., DESPREZ, J.D. & HOLDEN, W.D. (1955) Bacteriological study of portal-vein blood in man. *Archives of Surgery*, **61**, 404.
- THORBJARNARSON, B. (1958) Carcinoma of the intra-hepatic bile ducts. *Archives of Surgery*, **77**, 908.
- WARREN, K.W., ATHANASSIADES, S. & MONGE, J.I. (1966) Primary sclerosing cholangitis. *American Journal of Surgery*, **3**, 23.