Hepatol Int (2010) 4:653–658
DOI 10.1007/s12072-010-9205-3

CASE REPORT

Adult Langerhans cell histiocytosis and sclerosing cholangitis: a case report and review of the literature

Ibrahim Hatemi · Birol Baysal · Hakan Senturk · Kemal Behzatoglu · Erol Rustu Bozkurt · Gulsen Ozbay

Received: 8 June 2009 / Accepted: 13 July 2010 / Published online: 4 August 2010

Abstract
Background/aims Sclerosing cholangitis is a rare complication of Langerhans cell histiocytosis in children which can result in liver failure. This combination is even rarer in adults.
Case report We report a 65-year-old female who developed sclerosing cholangitis 4 years after the diagnosis of Langerhans cell histiocytosis.
Conclusion Sclerosing cholangitis caused by Langerhans cell histiocytosis is a rare condition in the adult population, but it has a high mortality. There is no definitive therapy other than liver transplantation. The long-term efficacy of liver transplantation remains unknown.

Keywords Langerhans cell histiocytosis · Sclerosing cholangitis

Introduction

Langerhans cell histiocytosis (LCH) is a disorder of unknown etiology characterized by proliferation of $CD1a^+$ dendritic cells [1]. It occurs mainly in children. Adult LCH is a quite rare disease with an incidence of 1–2 cases per million [1]. LCH may present as a single organ system disease or multi-organ system disease. In the single organ system disease, skin, lung and bone involvement are common. Skin involvement is the most common type of presentation and lung involvement is the most severe form of the disease. Liver involvement is reported in 10.1–18% of the pediatric patients with LCH [2, 3]. Sclerosing cholangitis (SC) was found in 1.3–6% of children with LCH [2, 3]. In adults, the combination of SC and LCH is rarely reported. There are 15 cases in the literature which are reviewed in this paper.

I. Hatemi (✉) · B. Baysal · H. Senturk · G. Ozbay
Division of Gastroenterology, Department of Internal Medicine, Istanbul University Cerrahpasa Medical Faculty, 34098 Aksaray, Istanbul, Turkey
e-mail: ihatemi@yahoo.com; ihatemi@istanbul.edu.tr

K. Behzatoglu · E. R. Bozkurt
Department of Pathology, Istanbul Education and Research Hospital, Abdurrahman Nafiz Gurman Caddesi Kocamustafapasa Fatih, Istanbul, Turkey

Case

A 65-year-old female was referred to our clinic with pruritus and elevated gamma-glutamyl transferase (GGT) level. Four years ago, she had had papular and pustular lesions and her skin biopsy revealed the diagnosis of LCH (Figs. 1, 2). Skin lesions disappeared with corticosteroid treatment but pruritus persisted. She also had diabetes and was using metformine and glimepiride. Physical examination revealed a palpable liver 4 cm below the costal margin. Laboratory analysis showed: ALT 45 U/l, AST 25 U/l, total bilirubin 0.76 mg/dl, conjugated bilirubin 0.21 mg/dl, alkaline phosphatase 177 U/l, GGT > 1543 U/l, albumin 2.1 g/dl, Ig G 1880 mg/dl (N: 700–1660), Ig M 137 mg/dl (N: 40–320), Ig A 353 mg/dl (N: 70–400), hemoglobin 13.2 g/dl, white blood cell count 10800/mm^3, platelets 274000/mm^3, protrombin time 10.2 s (107%), International normalized ratio (INR) 0.87. Serologic examination revealed: anti-HAV IgM (–), anti-HAV IgG (+), anti-HBc IgG (+), HBs Ag (–), Anti-HBs (+), anti-HCV (–), HCV-RNA (–), fluorescent antinuclear antibody (–), anti-smooth muscle antibody (–), anti-mitochondrial antibody (–). Radiological examination of the skull,

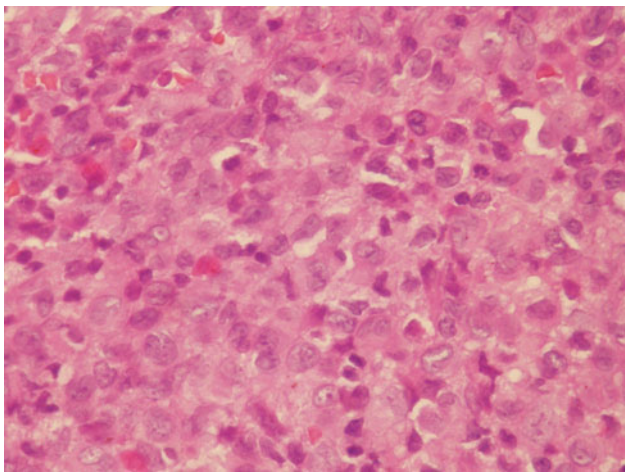

Fig. 1 Section of the skin biopsy specimen showing large mononuclear cells with oval cleaved nuclei and abundant cytoplasm infiltrating the dermis. There are also neutrophils and mononuclear cells on the background (Hematoxylin–eosin stain, ×400)

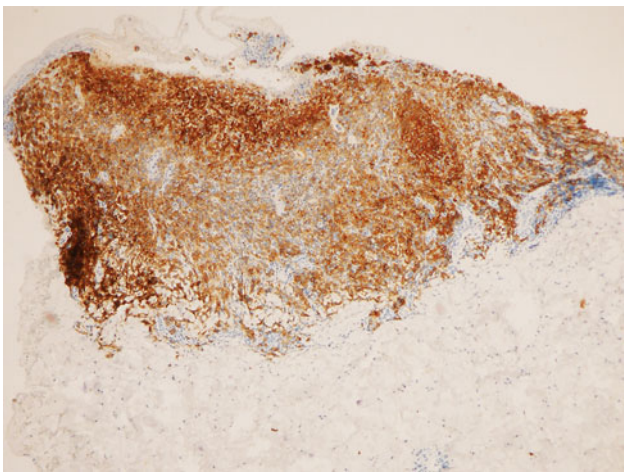

Fig. 2 Immunohistochemical stain. The Langerhans cell stains strongly for CD1a (×40)

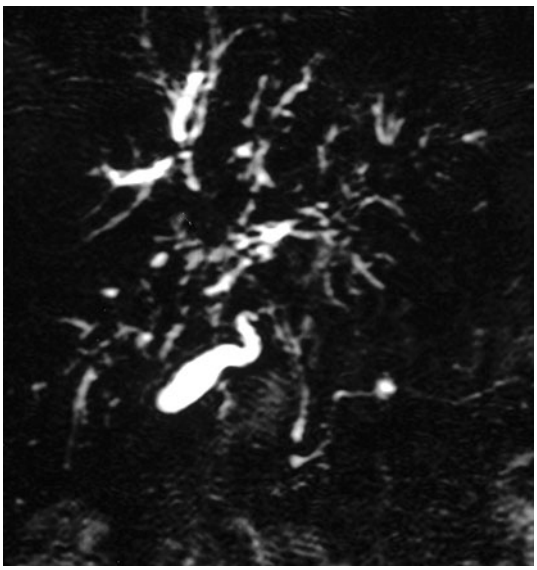

Fig. 3 Magnetic resonance cholangiopancreatography showing irregularities of intrahepatic ducts

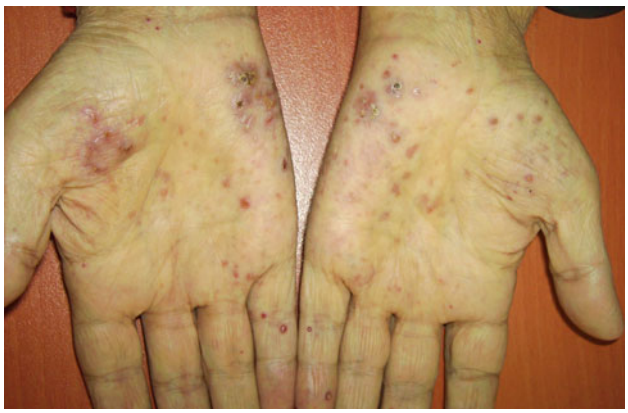

Fig. 4 Papular and pustular skin lesions

vertebrae and long bones, chest X-ray and cranial CT scan were normal. Magnetic resonance cholangiopancreatography (MRCP) showed slight irregularities of intrahepatic ducts (Fig. 3). Liver biopsy revealed only steatosis with normal portal areas and biliary tracts. She was then lost to follow up. One year later, she presented with jaundice. She had pruritic skin lesions on her palms (Fig. 4). Laboratory tests revealed: ALT 20 U/l, AST 35 U/l, GGT 157 U/l, alkaline phosphatase 252 U/l, total bilirubin 25.3 mg/dl, conjugated bilirubin > 15 mg/dl, INR 1.39, albumin 2.17 g/dl, hemoglobin 12.1 g/l, white blood cell count 15,200/mm^3. MRCP showed multifocal strictures and irregularity of the intrahepatic bile ducts. Endoscopic Retrograde Cholangiopancreatography revealed narrowing of the intrahepatic bile ducts and common bile duct, a plastic stent of 10 F diameter and 12 cm of length was inserted into common bile duct which had been obliterated. A second liver biopsy was performed which showed bile stasis, bile duct damage, ductular proliferation, mixed inflammation and mild fibrosis, but there was no Langerhans cell histiocyte infiltration (Figs. 5, 6). Immunohistochemical stain with CD1a which is a marker of Langerhans type dendritic cells was also negative. Histopathological findings were considered compatible with sclerosing cholangitis, however they were not definitely diagnostic. We discharged the patient with 1 g per day of ursodeoxycholic acid therapy. Eight months later, during her last control, she was still icteric and complaining of pruritus. Her laboratory tests revealed: ALT 69 U/l, AST 109 U/l, GGT 573 U/l, alkaline phosphatase 330 U/l, total bilirubin 13 mg/dl, conjugated bilirubin 10 mg/dl, INR 1, albumin 2.1 g/dl. She was still using ursodeoxycolic acid in the same dose.

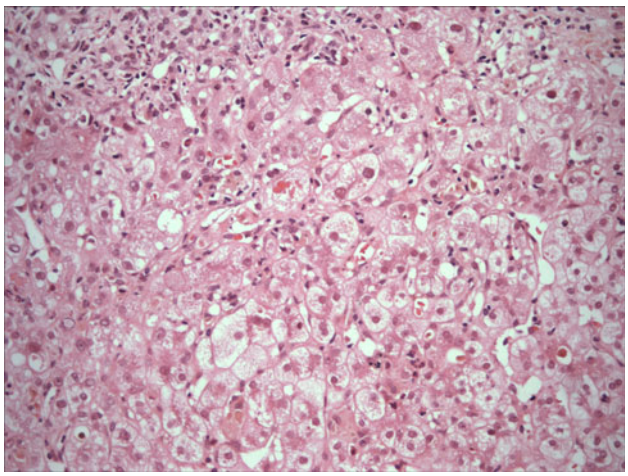

Fig. 5 Hepatic parenchymal cells show significant ballooning change. One of them contains Mallory bodies. On the *right corner*, there is a pseudoacinar formation. In the *middle*, there are canalicular bile plugs. On the *left upper part*, there is a portal area showing inflammatory infiltration and ductular proliferation (Hematoxylin–eosin, ×200)

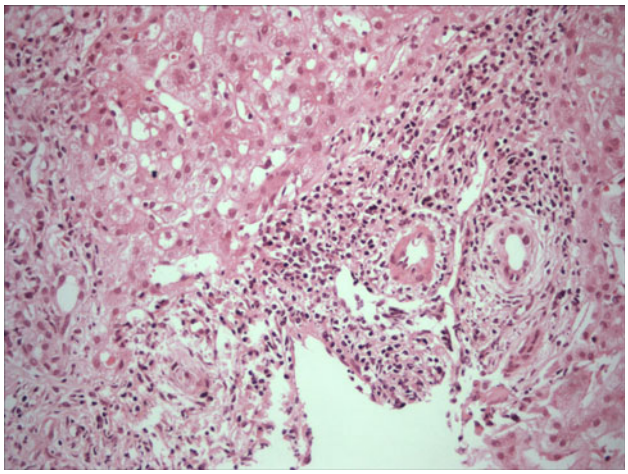

Fig. 6 There is a portal area showing chronic inflammatory changes. There is vacuolization and lymphocytic infiltration in the epithelial cells of a biliary canaliculus and increased periductal connective tissue around this canaliculus (Hematoxylin–eosin, ×200)

Discussion

The diagnosis of LCH is established by biopsy of lesions, histopathologic examination may show destructive granulomatous lesions containing mononuclear cells with indented nuclei. A definitive diagnosis requires that lesional cells show positive staining with CD1a antigen demonstrated by immnohistochemistry. LCH cells can also stain positive for CD-31, CD-68 or S100 [1]. In this case, positive staining for CD1a was demonstrated at skin biopsy (Fig. 2).

Lung, bone and skin involvement are common in adult patients with LCH [4]. This case with skin and liver involvement had no signs of another organ disease. Generally, liver involvement in LCH is a component of multisystem disease. Liver involvement can be categorized into two forms according to pathological findings: first, one is a portal tract inflammation without LCH infiltration and the second one is the infiltration of the portal tracts and bile ducts with LCH [5]. Hepatomegaly without signs of cholestasis may be reversible with medical treatment or sometimes spontaneously. Laboratory findings of cholestasis in a patient with LCH may reflect the damage of large or medium sized bile ducts. In these patients, the disease is usually chronic and progressive. Liver biopsy may demonstrate infiltration of the portal area and basement membrane of the bile ducts with LCH cells. Immunostaining for CD1a cells is required for the definitive diagnosis [5, 6]. As occurred in this case, liver biopsies that were not definitely diagnostic were reported frequently in pediatric patients [3]. This phenomenon is explained by the selective involvement of the major bile ducts by Langerhans cells which was not sampled in the biopsy specimen [6]. Another explanation is the timing of the biopsy procedure. If it is done after chemotherapy, Langerhans cells may have been destroyed. There is no standard treatment regime for SC in patients with LCH. Vinblastine/prednisolone therapy was successful in some pediatric patients [3]. Liver transplantation is required for progressive liver failure.

Data about adult patients with SC and LCH are given in isolated case reports (Table 1). There have been a total of 15 cases (8 female, 7 male) of adult LCH and SC reported. The mean age of these patients at the diagnosis of SC was 42.3 ± 17.1 years. In most of these patients, SC was a late complication of LCH. The mean period of time between the diagnosis of LCH and SC was 5.4 ± 6 years. However, in five patients the first manifestation of LCH was cholestatic liver disease. The liver biopsy showed histiocyte infiltration in 8 of these 15 patients. The specific histopathologic findings of LCH, such as CD1a or S100 positivity was reported in two patients. Four patients had liver transplantation, one of them also had a retransplantation, all of these four patients had remission after liver transplantation, but unfortunately, there is no data about the long-term prognosis of these patients. The rest of the patients died of liver failure or biliary sepsis, with two exceptions: one patient (case 10) who had remission after biliary bypass and chemotherapy with vincristine and the other one (case 6) who had remission after ursodeoxycolic acid and corticosteroid therapy. However, the long-term prognosis of these two patients also remains unknown. In six patients biliary by-pass procedures resulted in some improvements. Chemotherapy with vinblastine/vincristine

Table 1 Summary of adult cases with SC and LCH

	Age at the diagnosis of LCH/ sex	Organ involvement	Age at the diagnosis of SC (years)	Clinical findings	Liver biopsy findings	Treatment modalities	Prognosis of liver disease	Reference
1	57/F	Bone, pituitary gland, liver	65	Jaundice, fatigue, pruritus, elevated cholestatic liver enzymes	Chronic biliary tract pathology at the first biopsy. Histology of the native liver showed infiltration by Langerhans cells which were positive for S100 and CD1a	Right lobe split liver transplantation. Hepatic artery thrombosis on the post-operative day 4. Retransplantation with cadeveric whole organ	Normal liver function after 14 months following second transplantation	Griffiths et al. [7]
2	56/M	Skin, cerebellum, bone, liver	66	Pruritus, jaundice	Concentric fibrosis of peripheral bile ducts	Ursodeoxycolic acid for liver disease Vinblastine and corticosteroids for skin disease	Died with encephalopathy 16 months after the diagnosis	Desrame et al. [8]
3	41/F	Skin, pituitary gland, bone, liver, lung	42	Hepatomegaly, jaundice, elevated transaminase and cholestatic liver enzymes levels	Biliary cirrhosis	Liver transplantation, Methylprednisolone for skin disease	Remission of LCH after liver transplantation	Caputo et al. [9]
4	23/F	Lung, pituitary gland, liver, cerebellum	40	Jaundice pruritus hepatomegaly elevated transaminase and cholestatic liver enzymes	Compatible with sclerosing cholangitis	Supportive	Died of hepatic failure 18 months after the diagnosis	Gey et al. [10]
5	29/F	Pituitary gland, liver thyroid	31	Elevated transaminase and cholestatic liver enzymes	Chronic cholestasis with bile infarcts	Liver transplantation. Vinblastine and prednisolone for thyroid involvement	Remission of LCH after liver transplantation	Sampathkumar et al. [11]
6	44/M	Pituitary gland, lung bone, liver	56	Epigastric pain, weight loss, hepatomegaly	Concentric fibrosis of interlobulary bile ducts. Eosinophilic and mononuclear cells infiltration with histiocytes	Ursodeoxycolic acid 15 mg/kg and prednisolone 1 mg/kg	Improvement of SC	Pagnoux et al. [12]
7	24/M	Liver, lung, pituitary gland, stomach	28	Hepatomegaly, splenomegaly, Jaundice, elevated transaminase and cholestatic liver enzymes	First biopsy before liver transplantation: Edema of the portal tracts with an active chronic inflammatory cell infiltrate. Second biopsy at the reactivation period: Expansion of portal tracts densely infiltrated with histiocytes with CD1a and s-100 positive cells	LCH reactivation in the liver 4 years after orthotopic liver transplantation Vinblastine, etoposide and prednisolone were used with success	Disappearance of Langerhans cells and normal liver function tests after chemotherapy	de Diego et al. [13]
8	62/M	Liver	62	Biliary tract disease	Focal sinusoidal Langerhans cell infiltration and chronic cholestasis	Supportive	Died due to disease	Kaplan et al. [14]

Table 1 continued

	Age at the diagnosis of LCH/ sex	Organ involvement	Age at the diagnosis of SC (years)	Clinical findings	Liver biopsy findings	Treatment modalities	Prognosis of liver disease	Reference
9	18/F	Lung, pleura, pituitary gland, liver	18	Hepatomegaly, splenomegaly, weight loss, elevated transaminase and cholestatic liver enzymes levels	Micronodular cirrhosis with marginal and diffuse proliferation of bile ducts and moderate infiltration of fibrous septa by lymphocytes, histiocytes and eosinophils	Resolution of jaundice with Prednisolone and vinblastine first, but jaundice reoccurred	Died because of biliary septicemia	Pirovino et al. [15]
10	28/M	Lymph node, pituitary gland, bone, liver	43	Jaundice, abdominal pain, elevated transaminase and cholestatic liver enzymes levels	Marked periductal portal fibrosis, lymphocytic infiltrates mixed with histiocytes, diffuse intrahepatocellular cholestasis	Choledocotomy and roux-en-y hepaticojejunostomy, vincristine	Remission	Di Palo et al. [16]
11	26/F	Pituitarygland, lung, thyroid, liver	28	Jaundice, right upper quadrant pain, fever	Chronic inflammatory infiltrate and fibrosis, wall fibrosis of choledochus	T tube implantation, D-penicillamine 250 mg/day for 3 months with no benefit	NA	Ramos et al. [17]
12	44/F	Liver, skin	44	Jaundice, fatigue, epigastric pain	Dense infiltration with foamy histiocytes and eosinophils	Prednisone, radiotherapy, vinblastine without clinical improvement. Dilatation of the stricture of the right hepatic duct and T tube replacement at laparotomy. Progressive liver failure occurred	Fatal liver failure	Thompson et al. [18]
13	65/M	Liver, pituitary gland	65	Jaundice, pruritus	Biliary cirrhosis	Choledocojejunostomy without benefit. Progressive liver failure occurred	Fatal liver failure	Thompson et al. [18]
14	6/F	Bone, lymph node, lung, liver	17	Abdominal pain, jaundice	Secondary biliary cirrhosis	At laparoscopy gall bladder was found to be fibrotic and common bile duct strictured. Choledocojejunostomy, cholecystectomy, choledocolithotomy were performed. Four years later secondary biliary cirrhosis occurred	Fatal liver failure	Thompson et al. [18]
15	30/M	Liver, bone, lymph node, lung	30	Abdominal pain, jaundice, hepatomegaly, elevated transaminase and cholestatic liver enzymes levels	Portal and peri-portal fibrosis, infiltration of histiocytes	Pristinamycine prednisolone used with some clinical ameloriation, biliary by-pass (cholecysto jejunostomy) was necessary after 17 months	NA	Rogé et al. [19]

NA Not available

and corticosteroids was used in 3 patients (cases 2, 9 and 12) without clinical effects. One patient had reactivation of LCH, 4 years after liver transplantation. In this patient, the combination of vincristine, etoposide and corticosteroid was successful.

In our case with LCH, diagnosis of SC was suggested by radiological and histological findings. We did not try chemotherapy or corticosteroid treatment because the patient did not accept any therapy which has potential side effects.

As a result, SC caused by LCH is a rare condition in the adult population, but it has a high mortality. There is no definitive therapy other than liver transplantation. The long-term efficacy of liver transplantation remains unknown.

Conflict of interest None.

References

1. Stockschlaeder M, Sucker C. Adult Langerhans cell histiocytosis. Eur J Haematol 2006;76:363–368
2. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. Arch Dis Child 1996;75:17–24
3. Braier J, Ciocca M, Latella A, de Davila MG, Drajer M, Inventarza O. Cholestasis, sclerosing cholangitis, and liver transplantation in Langerhans cell Histiocytosis. Med Pediatr Oncol 2002;38:178–182
4. Aricò M, Girschikofsky M, Généreau T, Klersy C, McClain K, Grois N, et al. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. Eur J Cancer 2003;39:2341–2348
5. Guthery SL, Heubi JE. Liver involvement in childhood histiocytic syndromes. Curr Opin Gastroenterol 2001;17:474–478
6. Jaffe R. Liver involvement in the histiocytic disorders of childhood. Pediatr Dev Pathol 2004;7:214–225
7. Griffiths W, Davies S, Gibbs P, Thillainayagam A, Alexander G. Liver transplantation in an adult with sclerosing cholangitis due to Langerhans cell histiocytosis. J Hepatol 2006;44:829–831
8. Desrame J, Béchade D, Defuentes G, Goasdoue P, Raynaud JJ, Claude V, et al. Langerhans cell histiocytosis in an adult patient associated with sclerosing cholangitis and cerebellar atrophy. Gastroenterol Clin Biol 2005;29:300–303
9. Caputo R, Marzano AV, Passoni E, Fassati LR, Agnelli F. Sclerosing cholangitis and liver transplantation in Langerhans cell histiocytosis: a 14-year follow-up. Dermatology 2004;209:335–337
10. Gey T, Bergoin C, Just N, Paupard T, Cazals-Hatem D, Xuan KH, et al. Langerhans cell histiocytosis and sclerosing cholangitis in adults. Rev Mal Respir 2004;21:997–1000
11. Sampathkumar S, Younger C, Cramer H, Chalasani N, Skierczynski PA. Langerhans' cell histiocytosis involving the pituitary, thyroid, lung, and liver. Endocr Pract 2002;8:217–221
12. Pagnoux C, Hayem G, Roux F, Palazzo E, Meyer O. Sclerosing cholangitis as a complication of Langerhans'cell histiocytosis. Rev Med Int 2003;24:324–327
13. de Diego A, Escudero M, Catalina MV, Salcedo M, Garcí Sánchez A, Alvarez E, et al. Recurrence of Langerhans cell histiocytosis in the graft after liver transplantation in adults. Transplant Proc 2002;34:1245–1247
14. Kaplan KJ, Goodman ZD, Ishak KG. Liver involvement in Langerhans' cell histiocytosis: a study of nine cases. Mod Pathol 1999;12:370–378
15. Pirovino M, Jeanneret C, Läng RH, Luisier J, Bianchi L, Spichtin H. Liver cirrhosis in histiocytosis X. Liver 1988;8:293–298
16. Di Palo S, Faravelli A, Beretta E, Taccagni GL. Langerhans histiocytosis of the choledochus in an adult patient with a history of disseminated disease. Tumori 1988;74:593–597
17. Ramos FJ, Pérez-Arellano JL, López-Borrasca A. Primary sclerosing cholangitis in histiocytosis X. Am J Med 1987;82:191
18. Thompson HH, Pitt HA, Lewin KJ, Longmire WP Jr. Sclerosing cholangitis and histiocytosis X. Gut 1984;25:526–530
19. Rogé J, Testas P, Durand B, Amat D, Camilléri JP, Roche A, et al. Sclerosing cholangitis and histiocytosis X. Report of a case. Gastroenterol Clin Biol 1981;5:620–627