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CASE REPORT

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A case of inflammatory pseudotumour of the common bile duct

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Abstract Inflammatory pseudotumour of the common bile duct (CBD) is extremely rare. A 58-year-old Japanese female without choledocolithiasis underwent pancreatico-duodenectomy for constriction of the middle lower region of the CBD. A submucosal tumour protruding into the CBD, was histologically inflammatory consisting of fibroblastic cells, collagen fibres and myxoid stroma with chronic inflammatory cells. This lesion was surrounded by an irregular fibrosclerosing lesion with obliterative phlebitis which involved the neighbouring pancreas and lymph nodes. Clonal analysis of the tumour by polymerase chain reaction analysis of X chromosome inactivation patterns, confirmed the polyclonal nature of the lesion. Immunohistochemically, the fibroblastic cells in both lesions had the same phenotype [vimentin (+), desmin (–), muscle-specific actin (–) and CD34 (+)] suggesting that these lesions with different histological features represent zonation of the same inflammatory process. The outer lesion extended irregularly into adjacent pancreatic tissue and lymph nodes. This fact made it difficult to differentiate this from a malignant lesion, even if frozen sections contained no atypical cells.

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Introduction

Inflammatory pseudotumour (IPT) may present as a mass in pulmonary and extrapulmonary tissues [3–5, 7, 9–11, 14, 18, 22–24]. IPT is a morphologically similar entity that consists of heterogeneous types; some cases may represent benign or low-grade malignant myofibroblastic tumours [5], and others are distinctly reparative lesions, especially in the urogenital tract [11, 13]. Although IPT occurs in practically every conceivable site in the body, it has rarely been documented in the extrahepatic bile ducts [9, 10, 18, 23]. In the present paper, we describe such a lesion in the common bile duct (CBD) in a Japanese female. An interesting finding was that the IPT was surrounded by a fibrosclerosing lesion in the neighbouring tissue. Clonal analysis and immunohistochemistry were used to characterize the fibroblasts in the IPT and the accompanying fibrosclerosing lesion.

Clonality can be assessed in any cell lineage in most female subjects by molecular analysis of patterns of X chromosome inactivation [1, 17]. Several monoclonal antibodies are also now available for characterizing spindle cells in neoplastic and non-neoplastic lesions. A monoclonal antibody against CD34, which is thought to be specific for human haematopoietic progenitor cells, labels a specific population of fibroblastic cells [19]. These analyses are probably useful for further classification of this unusual tumour-like lesion of intriguing histology.

Case report

Clinical findings

A 58-year-old female was admitted to Kanto Teishin Hospital for an evaluation of liver dysfunction. She had a history of four surgical operations; appendectomy at the age of 19, haemorrhoidecto-

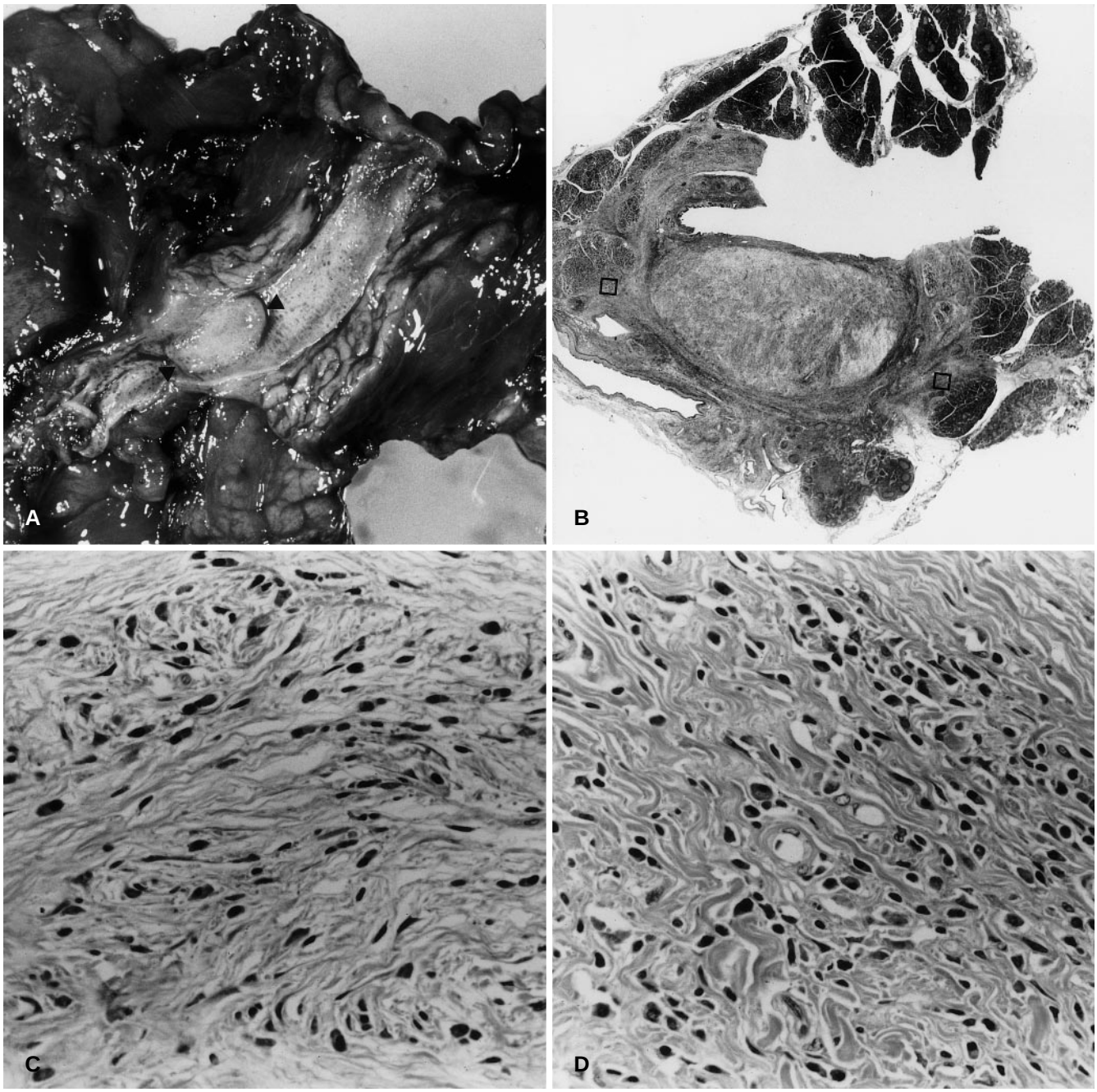

Fig. 1A Gross features of the lesion of the common bile duct, showing a low protrusion with a smooth surface. **B** Cross-section of the lesion. Two features are seen; a tumour-like, relatively well-defined lesion, and diffuse, irregular shaped fibrous lesions extending to the surrounding parenchyma (*box*). Although both of the lesions are composed of fibrous spindle cells with plasma cell and lymphocyte infiltration, the former area has relatively more myxoid stroma (**C**) and the latter is more collagenous (**D**). (**C** and **D** Haematoxylin and eosin stain, original magnification ×320)

my at the age of 23, and hysterectomy for leiomyoma uteri and excision of pulmonary sclerosing haemangioma at the age of 57. There was no history of inflammatory bowel disease or any autoimmune disease. She usually drank two glasses of beer per day. Laboratory tests revealed serum bilirubin 0.7 mg/dl, alkaline phosphatase 653 U/l (normal, 80–250 U/l), glutamic oxalacetic transaminase 159 U/l (<d35 U/l), glutamic pyruvic transaminase 454 U/l (<40 U/l) and γ-glutamyl transpeptidase 331 U/l (<50). Serum IgG was slightly increased (2,008 mg/dl, normal 1,180–1,654 mg/dl), but tests for antinuclear antibodies and anti-mitochondrial antibody were negative. Hepatitis B virus antigen and anti-chronic hepatitis C virus antibody were negative. Tumour markers, including alpha-fetoprotein, carcinoembryonic antigen and CA19-9, were within normal limits. A retrograde cholangiopancreatography showed marked narrowing of the middle-lower region of the CBD, 2.2 cm in length. Endoscopic ultrasonogram revealed a hypoechoic nodule, 2.0 cm in diameter, at the narrowed portion of the CBD. Liver biopsy showed non-specific chronic inflammation in the portal tract. Pancreato-duodenectomy was performed with a presumed diagnosis of carcinoma of the CBD. After the operation, liver function returned to normal.

Materials and methods

The formalin-fixed, paraffin-embedded sections were subjected to immunohistochemistry to characterize the fibroblasts in IPT and the fibrosclerosing lesion, using the avidin biotin complex method. The antisera used were against vimentin (Dako, Tokyo, Japan), muscle-specific actin (HHF-35, Enzo Diagnostics, New York, USA), desmin (Immunotech, Marseilles, France), S-100 protein (Dako), CD34 (Nichirei, Tokyo, Japan), CD21 (Dako), CD35 (Dako) and MIB1 (Ki67, Immunotech). A labelling index was calculated as the number of labelled nuclei as a percentage of the total nuclei counted. We counted a total of 1,000 nuclei of fibroblastic spindle cells in the tumour-like lesion using a printed photograph. Epstein-Barr virus (EBV)-encoded small RNA (EBER) in situ hybridization was also applied to the formalin-fixed, paraffin-embedded sections, as reported previously [8].

The methods used to assess the clonality of cells from a female subject follow the principle of lyonization. A polymerase chain reaction (PCR)-based method that can detect polymorphisms at a particular X-linked locus allows for a distinction to be made between the maternal and paternal X chromosomes [1, 17]. An active X chromosome can be distinguished from an inactive X chromosome by its state of methylation. Thus, by combining these analyses we can determine patterns of X chromosome inactivation [1, 17]. If the lesion is neoplastic, a monoclonal or clonal population of cells should inactivate one X chromosome exclusively. Two X-linked polymorphic loci were used to analyse clonality: the loci for phosphoglycerate kinase (PGK) and X-linked human androgen receptor (HUMARA). The analyses were performed as described previously [1, 17]. Briefly, DNA samples of the tumour-like lesion were subjected to PCR to amplify the PGK and HUMARA genes by using a set of oligonucleotide primers, either after digestion with *Hpa*II or directly without digestion. The PCR products of the PGK gene were then digested with *Bst*XI to reveal restriction fragment length polymorphism, electrophoresed in 2% agarose and visualized with ethidium bromide and ultraviolet light. PCR for the HUMARA gene was performed using biotinylated primers. The amplified products were electrophoresed in 4% polyacrylamide gel containing 30% formamide and 4M urea, transferred to a nylon membrane, and detected with chemiluminescence.

Pathological findings

A low protruding lesion (1.7×1.0 cm) was located at the middle portion of the CBD, and was covered by intact ductal mucosa (Fig. 1A). The CBD was slightly dilated above the lesion. The cut surface showed a relatively well circumscribed and grey-white tumour-like lesion, which compressed the lumen of the CBD eccentrically. A diffuse and irregular fibrosing lesion surrounded the tumour-like swelling and extended into the adjacent pancreas and lymph nodes (Fig. 1B). Histologically, the tumour-like lesion was composed of fibroblastic spindle cells, fine collagen fibres and myxoid matrix with chronic inflammatory cells and small numbers of eosinophils (Fig. 1C). The fibroblastic spindle cell bundle showed an irregular stream. The cellularity of the spindle cells was uneven, but there were no foci of compact spindle cell proliferation. Mitotic figures and nuclear atypia were not observed in the fibroblastic cells. The glands of the bile duct wall adjacent to the lesion was markedly decreased. Although lymphoid follicule formation was observed, necroinflammatory changes were not seen in the CBD wall without tumour tissue. The surrounding irregular fibrosing lesion contained more hyaline collagen fibres than the area of the tumour-like lesion, and was also accompanied by chronic inflammatory cells (Fig. 1D). "Phlebitis" was observed within the area of the fibrosclerosing lesion (Fig. 2). The borderline between the tumour-like and the fibrosing lesions was relatively clear, but there was no capsule. The lesion was histologically consistent with IPT, and the surrounding fibrosclerosing lesion histologically resembled retroperitoneal fibrosis. The stomach, duodenum and gall bladder showed no abnormalities. No acid-fast bacilli or fungi were seen.

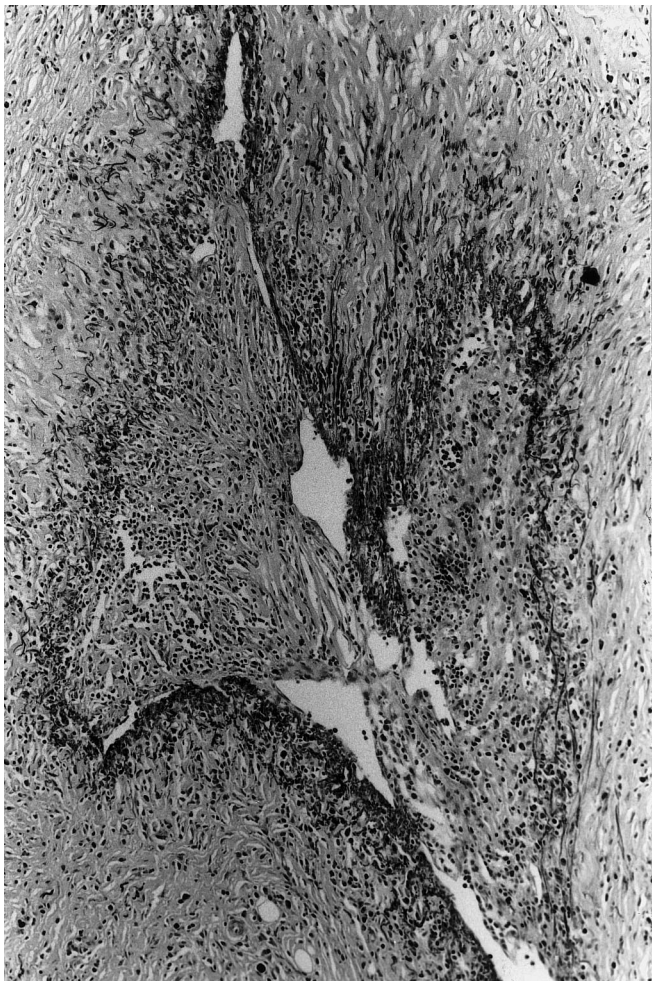

Fig. 2 Small veins around the common bile duct show almost complete obliteration, with prominent inflammatory cell (mainly mononuclear round cells) infiltration and fibrosis. Elastica-Masson stain, original magnification ×80)

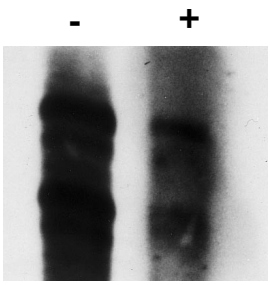

Fig. 3 Results of the human androgen receptor assay. The left lane is undigested template; the right lane is the polymerase chain reaction product of *Hpa*II-digested DNA from the lesion. Clonality analysis showed a polyclonal pattern

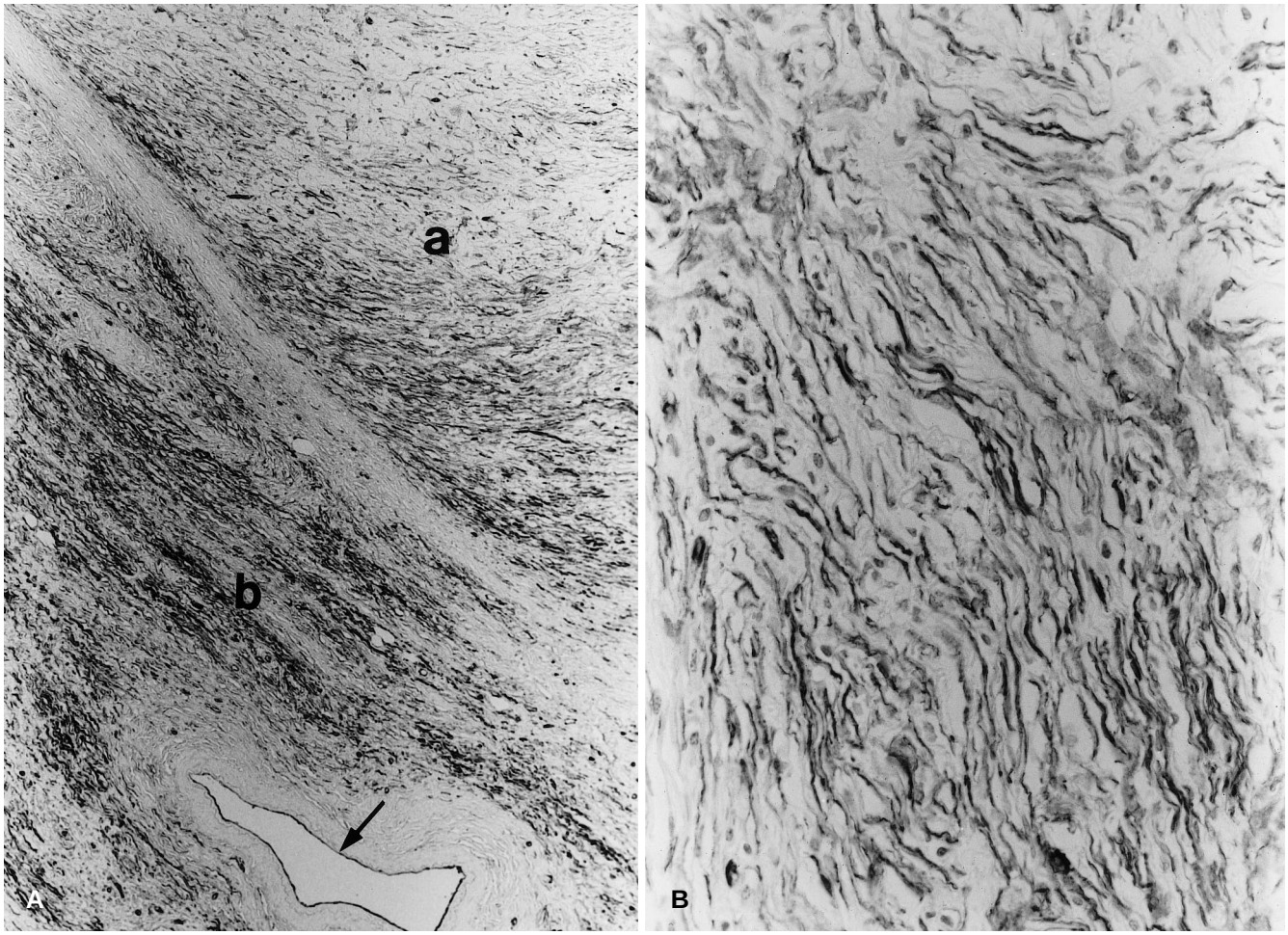

Fig. 4A, B CD34 expression is observed in spindle cell of both the tumour-like lesion (*a*) and the surrounding diffuse lesion (*b*). CD34 is also positive at the endothelium of the small artery **(A**; *arrow*). Close-up view of the pseudotumour lesion (**B**). (Original magnifications: left ×32; right ×320)

Clonal analysis, using the HUMARA gene on the X chromosome, revealed a polyclonal pattern of inactivation in the tumour-like lesion. The electrophoresed pattern of the amplified DNA fragment of the HUMARA gene with previous digestion with *Hpa*II was identical to that without such digestion (Fig. 3). As for the PGK gene, the patient was homozygous for the *Bst*XI-restriction site, and the analysis could not be performed.

Proliferating fibroblastic cells in both IPT and the fibrosclerosing lesion of the present case were strongly and diffusely positive for vimentin and CD34 (Fig. 4), but were negative for desmin, muscle-specific actin and S-100 protein. There was no positive signal for EBER. The labelling index with MIB1 was 2.6%.

Discussion

IPT is a mass lesion which exhibits a common histology: a variable admixture of bland-looking spindle cells, chronic inflammatory cells and collagen fibres [3–5, 7, 9–11, 14, 18, 22–24]. However, what has been previously reported in the literature as IPT is now considered to be heterogeneous [3, 5]. "IPT" has been loosely applied to inflammatory (true) neoplasms which should be appropriately excluded from IPT, such as inflammatory follicular dendritic cell tumours (usually in the liver or spleen) [21], and myofibroblastic neoplasms including inflammatory fibrosarcoma [15]. In the present case, mitotic figures were extremely rare and the labelling index with the monoclonal antibody MIB1 (Ki67) was low in the fiboblastic cells of the tumour-like lesion. The clonal analysis, which is based on random X chromosome inactivation, did not disclose a clonal component. CD21 and CD35, markers for follicular dendritic cell, were both negative. Although EBv was recently identified in some leiomyomatous or follicular dendritic cell tumours [2, 20, 21], a sensitive method of EBER in situ hybridization did not identify a positive signal. These facts indicate that the lesion in the present case is not a neoplasm, but is rather an inflammatory or reparative type of IPT.

In the present case, the lesion was surrounded by a fibrosclerosing mass with obliterative phlebitis. It is possible that the submucosal tumour-like lesion may have been caused by vascular lesions in the outer fibrosclerosing lesion. CD34 was expressed in the fibroblastic cells

Table 1 Reported cases of inflammatory pseudotumour of the common bile duct (*CBD* common bile duct)

Case	Author	Age (years)	Sex	Size (cm)	Location/extension	Involvement of systemic organs
1	E.E. Haith et al. [9]	6	M	3 cm in diameter	Lower portion of the CBD/ pancreas and a few nearby lymph nodes	–
2	J.D. Stamatakis et al. [23]	13	F	3 cm in diameter	Upper portion of the CBD/ cystic duct and common hepatic duct	–
3	H. Ikeda et al. [10]	43	M	No mass formation	CBD, gall bladder, cystic duct and lymph nodes	Lung, bilateral, cevical and inguinal regions
4	Y. Ozeki et al. [18]	73	M	2.1×1.9×1.5 cm	Upper portion of CBD/ hepatic hilus	–
5	Present case	58	F	1.7×1.0×1.0 cm	Middle portion of the CBD/ pancreas and lymph nodes	–

of both lesions in the present case. In a case of chronic cholangitis due to a bile stone, which was examined for a control study, CD34-positive cells were observed only in the endothelium of the small vessels and in only a limited area of the outer layer of the fibrous wall (n=8). These facts indicate that the fibroblastic cells in both lesions may be induced at the same site, and that both lesions were histological variations of a common inflammatory and fibrosing process. Coffin et al. referred to this phenomenon as zonation in IPT [5]. In IPT of the urinary bladder, spindle cells were immunoreactive with CD34 in only 1 of 12 cases, in which muscle-specific actin was negative [13]. It would also be interesting to determine whether phenotypic analysis of the spindle cells (muscle-specific actin (–) and CD34 (+) in the present case) could be useful for further classification of IPT.

IPT or IPT-like lesions in the common bile duct have rarely been reported [9, 10, 18, 24]. Four other cases have been classified as IPT of the common bile duct in the English and Japanese literature (Table 1). The case reported by Ikeda et al. showed granulomatous lesions in the bilateral hepatic ducts, extrahepatic bile ducts and gall bladder, as well as in the lymph node and the lung, with a positive serum immune complex and a decreased complement level [10]. This case appeared to represent a different type of disease, perhaps a lymphoplasmacytic variant of primary sclerosing cholangitis [12] or multifocal fibrosclerosis [6]. The tumour-like lesions of the four other cases, including ours, have been restricted to the CBD (Table 1). IPT of the CBD is also different from the hepatic IPT associated with chronic cholangitis reported by Nakanuma et al. [16], not only in its location but also in its aetiology, since necroinflammatory or necrodegenerative changes in hepatic IPT were not observed in the peribiliary glands in IPT of the CBD.

This tumour-like lesion of the common bile duct with the outer fibrosing lesion found in the present case involved the pancreas and lymph nodes irregularly, mimicking carcinomatous infiltration. This fact made it difficult to decide upon appropriate treatment at operation, and would have done so even if frozen sections had indicated a benign process.

References

1. Allen RC, Zoghbi HY, Moseley AB, Rosenblatt HM, Belmont JW (1992) Methylation of *Hpa*II and *Hpa*I sites near the polymorphic CAG repeat in the human androgen-receptor gene correlates with X chromosome inactivation. Am J Hum Genet 51:1229–1239
2. Arber DA, Kamel OW, Rijn M van de, Davis RE, Medeiros LJ, Jaffe ES, Weiss LM (1995) Frequent presence of the Epstein-Barr virus in inflammatory pseudotumor. Hum Pathol 26:1093–1098
3. Chan JKC (1996) Inflammatory pseudotumor: a family of lesions of diverse nature and etiologies. Adv Anat Pathol 3:156–171
4. Chen KTK (1992) Mycobacterial spindle cell pseudotumor of lymph nodes. Am J Surg Pathol 16:276–282
5. Coffin CM, Watterson J, Priest JR, Dehner LP (1995) Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol 19:859–872
6. Comings DE, Skubi KB, Eyes JV, Motulsky AG (1967) Familial multifocal fibrosclerosis-Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease. Ann Intern Med 66:884–892
7. Facchetti F, De Wolf Peeters C, De Wever I, Frizzera G (1990) Inflammatory pseudotumor of lymph nodes, immunohistochemical evidence for its fibrohistiocytic nature. Am J Pathol 137:281–289
8. Fukayama M, Hayashi Y, Iwasaki Y, Chong J, Ooba T, Takizawa T, Koike M, Mizutani S, Miyaki M, Hirai K (1994) Epstein-Barr virus-associated gastric carcinoma and Epstein-Barr virus infection of the stomach. Lab Invest 71:73–81
9. Haith EE, Kepes JJ, Holder TM (1964) Inflammatory pseudotumor involving the common bile duct of a dix-year-old boy: Successful pancreatico-duodenectomy. Surgery 56:436– 441
10. Ikeda H, Oka T, Imafuku I, Yamada S, Yamada H, Fujiwara K, Hirata M, Idezuki Y, Oka H (1990) A case of inflammatory pseudotumor of the gallbladder and bile duct. Am J Gastroenterol 85:203–206
11. Jones EC, Clement PB, Young RH (1993) Inflammatory pseudotumor of the urinary bladder. A clinicopathological immunohistochemical, ultrastructural, and flow cytometric study of 13 cases. Am J Surg Pathol 17:264–274
12. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N (1991) Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Hum Pathol 22:387–395
13. Lundgren L, Aldenborg F, Angervall L, Kindbom LG (1994) Pseudomalignant spindle cell proliferation of the urinary bladder. Hum Pathol 25:181–191

14. Matsubara O, Tan-Liu NS, Kenney RM, Mark EJ (1988) Inflammatory pseudotumors of the lung, progression from organizing pneumonia to fibrous histiocytoma or to plasma cell granuloma in 32 cases. Hum Pathol 19:807–814
15. Meis JM, Enzinger FM (1991) Inflammatory fibrosarcoma of the mesentery and retroperitoneum. A tumor closely simulating inflammatory pseudotumor. Am J Surg Pathol 15:1146–1156
16. Nakanuma Y, Tsuneyama K, Masuda S, Tomioka T (1994) Hepatic inflammatory pseudotumor associated with chronic cholangitis: Report of three cases. Hum Pathol 25:86–91
17. Noguchi S, Motomura K, Inaji H, Imaoka S, Koyama H (1992) Clonal analysis of human breast cancer by means of the polymerase chain reaction. Cancer Res 52:6594–6597
18. Ozeki Y, Matsubara N, Saiga T, Ishida H, Kimura T, Yasumura M, Fujita S (1993) Inflammatory tumor of the hepatic hilus mimicking bile duct cancer. Report of a case (in Japanese). Nippon Geka Gakkai Zasshi 94:1064–1067
19. Rijn M van de, Lombard CM, Rouse RV (1994) CD34 A review. Appl Immunohistochem 2:71–80
20. Selves J, Meggetto F, Brousset P, Voigt J-J, Pradère B, Grasset D, Icart J, Mariamé B, Knecht H (1996) Inflammatory pseudotumor of the liver. Evidence for follicular dendritic reticulum cell proliferation associated with clonal Epstein-Barr virus. Am J Surg Pathol 20:747–753
21. Shek TWH, Ho FCS, Ng IOL, Chan ACL, Ma L, Srivastava G (1996) Follicular dendritic cell tumor of the liver. Evidence for an Epstein-Barr virus related clonal proliferation of follicular dendritic cell. Am J Surg Pathol 20:313–324
22. Someren A (1978) “Inflammatory pseudotumor” of liver with occlusive phlebitis, report of a case in a child and review of the literature. Am J Clin Pathol 69:176–181
23. Stamatakis JD, Howard ER, Williams R (1979) Benign inflammatory tumour of the common bile duct. Br J Surg 66:257–258
24. Thomas RM, Jaffe ES, Zarate-Osorno A, Medeiros LJ (1993) Inflammatory pseudotumor of the spleen, a clinicopathologic and immunophenotypic study of eight cases. Arch Pathol Lab Med 117:921–926