

Cholangiocarcinoma Complicating Secondary Sclerosing Cholangitis from Cryptosporidiosis in an Adult Patient with CD40 Ligand Deficiency: Case Report and Review of the Literature

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Established Facts

- CD40 ligand (CD40L) deficiency is usually known as a disease of childhood with a shortened life expectancy prior to bone marrow transplantation although it may be diagnosed late in adulthood as published recently [1].
- Cholangiocarcinoma has been known to occur in children with CD40L deficiency.
- Prompt diagnosis of cryptosporidial infection in patients with CD40L deficiency is crucial as current antimicrobial therapy for this infection is not adequate for eradication and patients need to be referred for bone marrow transplantation to restore T cell function for any chance of survival.

Novel Insights

- Cholangiocarcinoma arising from secondary sclerosing cholangitis in association with cryptosporidiosis in an adult with CD40L deficiency has not been described previously.
- The mutation in CD154 (T245M substitution) does not appear to be a milder phenotype of CD40L deficiency as previous literature has suggested.
- The risk of cryptosporidiosis is life-long.

Key Words

Hyper-immunoglobulin M syndrome • CD40 ligand deficiency • Cryptosporidial infection • Sclerosing cholangitis • Cholangiocarcinoma

Abstract

A 43-year-old man with a hyper-immunoglobulin M syndrome due to CD40 ligand deficiency presented with insidious onset of recurrent diarrhoea and deranged liver function tests. Standard stool microscopy was repeatedly

negative for cryptosporidia but immunofluorescent testing and polymerase chain reaction demonstrated the presence of infection eventually. Despite both paromomycin and nitazoxanide, he developed sclerosing cholangitis secondary to cryptosporidial infection. Whilst being considered for dual bone marrow and liver transplantation, he was found to have cholangiocarcinoma on imaging after three biopsies of a suspicious lesion. This is a rare complication of this combined immune deficiency predominantly in children that has not been reported previously in a long-term survivor with this condition.

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Introduction

Individuals with CD40 ligand (CD40L) deficiency who acquire chronic *Cryptosporidium parvum* infection are at a major risk of developing severe liver disease with sclerosing cholangitis [2]. Children with CD40L deficiency have been known to develop sclerosing cholangitis associated with cryptosporidium infection [3, 4]. However, the development of cholangiocarcinoma arising from sclerosing cholangitis secondary to cryptosporidial infection has not been previously reported in an adult with this combined immune deficiency.

CD40L deficiency can be complicated by various gastrointestinal cancers including neuroendocrine carcinoma [5]. Hayward et al. [6] described cholangiocarcinoma, hepatocellular carcinoma, and adenocarcinoma in a cohort of 9 boys with CD40L deficiency and cholangiopathy. Two out of the 9 boys developed fatal cholangiocarcinoma and did not survive past the third decade [6]. In this study, 70% of the boys who were screened for infection had *C. parvum* infection, but it is unclear if these were the boys who developed cholangiocarcinoma [6]. These complications have been described previously in children, but here we present an adult man with CD40L deficiency who developed chronic *C. parvum* later in life and ultimately died from cholangiocarcinoma.

Case Report

A 35-year-old man with CD40L deficiency was referred in 1992 after a severe reaction to intramuscular immunoglobulin (IMIG), in order to change to intravenous immunoglobulin (IVIG) therapy. He first presented aged 2 years with severe pneumonia presumed to be *Pneumocystis carinii* infection and underwent a lobectomy. Subsequently he was diagnosed with CD40L deficiency with low levels of serum IgG (2.2 g/l) and IgA (<0.1 g/l) but a raised level of immunoglobulin M (IgM; 5.0 g/l). He received replacement IMIG twice weekly until 1992 and remained well, although he was extremely needle phobic and only allowed a few people to administer IMIG.

At the first consultation in Oxford he reported a history of intermittent diarrhoea associated with IMIG injections. Examination was unremarkable. However, his liver function tests (LFTs) were elevated with γ -glutamyl transpeptidase of 131 IU/l (normal range: 15–40) and alkaline phosphatase of 461 IU/l (normal range: 80–250). Viral serology (including HIV and HCV) and stool microscopy/culture were negative. A liver ultrasound scan (USS) was normal and the abnormalities in LFTs were thought to be related to current antidepressant medication. Meanwhile the mutation in *CD154* was identified as T254M substitution in 1996.

Two years later he felt constantly tired and developed transient diarrhoea the day after IVIG. LFTs showed a fluctuating cholestatic pattern. Following the first review of the registry for CD40L

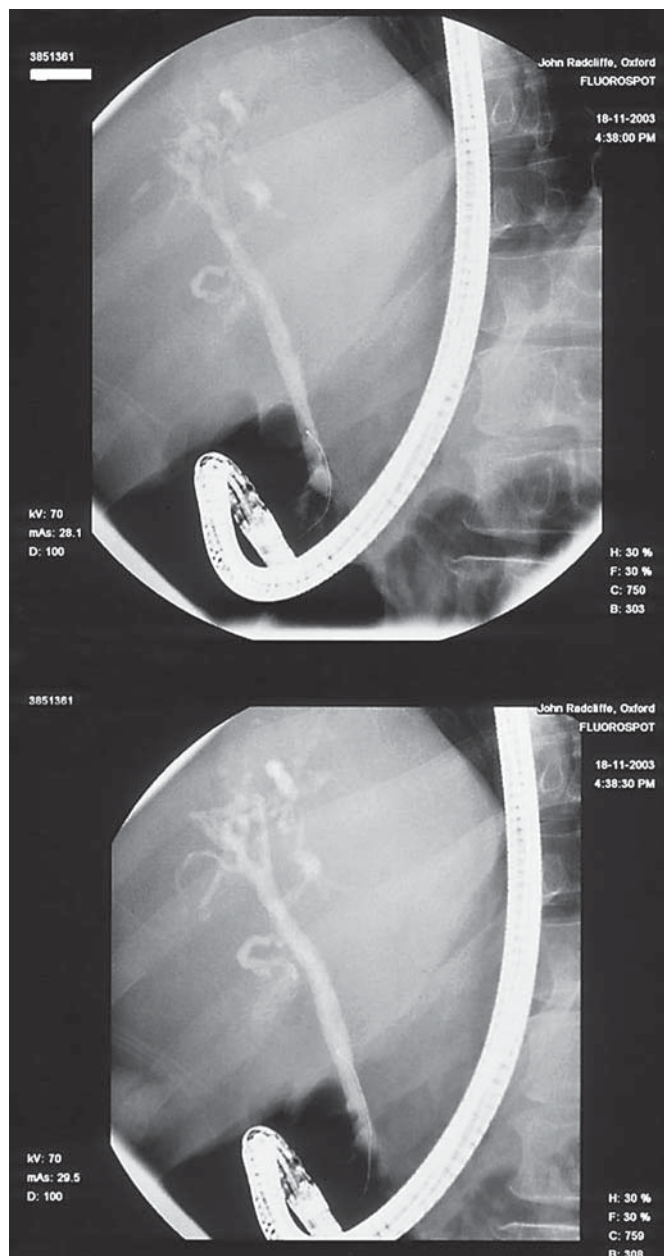


Fig. 1. ERCP showing abnormal intrahepatic ducts, irregularity of the common bile duct and cystic dilatation within the biliary tree.

deficiency patients in 1997 and the finding that the presence of the CD40L protein on T cells was essential for the removal of these organisms in mice in 1998, there was again concern about cryptosporidial infection, although stool samples had been negative by light microscopy. He was advised to boil water for ingestion and, as he was a plumber, the need for protective clothing and gloves was reinforced.

In 2000 he was referred to hepatologists to investigate abnormal LFTs that persisted despite stopping antidepressants. An abdominal USS revealed increased periportal echogenicity and a thickened gall bladder wall with a small polyp in the fundus. The common bile duct was mildly dilated at 0.67 cm at the porta with normal intrahepatic ducts. He underwent an MR cholangiopancreatography that revealed typical changes of sclerosing cholangitis, mainly involving the intrahepatic bile ducts. Three monthly stool samples remained negative for cryptosporidia by standard microscopy.

He commenced ursodeoxycholic acid 500 mg b.d. and initially his LFTs improved but in 2001 his alkaline phosphatase rose acutely to 1,453 IU/l from 459 IU/l and γ -glutamyl transpeptidase to 297 IU/l from 96 IU/l. A few months later he developed steatorrhoea, itching and significant weight loss. Immunofluorescence and polymerase chain reaction testing for cryptosporidia in stools were now available and samples were positive. He was started on paromomycin 1 g b.d. for 6 months and azithromycin 500 mg o.d. for 2 months. Unfortunately the cryptosporidial infection could not be eradicated despite further courses of paromomycin and azithromycin.

Bone marrow transplantation (BMT) was now considered, as reconstitution with normal T cells was the only method likely to eradicate this infection [7], even though BMT at this age was a considerable risk. Prior to referral for BMT, repeat USS showed some mild dilatation of the intrahepatic ducts with a stricture possibly at the hilum and an endoscopic retrograde cholangiopancreatography was recommended. In October 2003 he was admitted with oesophageal variceal bleeding; although the varices were successfully banded endoscopically he developed further complications of advanced liver disease with ascites, spontaneous bacterial peritonitis and encephalopathy. An endoscopic retrograde cholangiopancreatography showed abnormal intrahepatic ducts, irregularity of the common bile duct and cystic dilatation within the intrahepatic biliary tree. The changes were in keeping with secondary sclerosing cholangitis with the associated finding of cryptosporidia in stool (fig. 1). Subsequent liver biopsy confirmed secondary sclerosing cholangitis and established cirrhosis. In view of these findings he was referred for both liver transplantation and BMT.

Two months later he was readmitted with cholangitis and transferred to King's College Liver Unit for transplant assessment. A CT scan of the liver revealed a suspicious area in the right lobe. A liver biopsy showed features of cholangiopathy and moderate fibrosis of the portal tracts with extensive patchy portal bridging fibrosis. A USS in February 2004 showed a large solid hypodense lesion in the right lobe and the right portal vein appeared thrombosed. Following this, a diagnosis of cholangiocarcinoma was made on the third biopsy and he died a month later.

Discussion

X-linked hyper-IgM syndrome is a rare genetic primary immunodeficiency disease caused by mutations of the CD40L gene (*CD154*). It is characterized by normal or elevated IgM levels, reduced levels of IgG, IgA and IgE, and defective T cell function [3, 8] in boys [9]. Individuals are susceptible to recurrent bacterial and opportunistic

infection such as *P. carinii* and *C. parvum*, often presenting in their first year of life [10].

Levy et al. [11] estimated that 75% of patients develop liver-related complications and the risk may be cumulative as with our patient [8, 10]. Treatment is mainly based upon administration of therapeutic immunoglobulin, antibiotics for infections, and steroids used to treat neutropenia or severe autoimmune manifestations [11]. Allogeneic haematopoietic stem cell transplantation (HSCT) offers the only possibility of cure [12, 13] and is now standard treatment for newly diagnosed young patients in most centres. However, the better outcome for HSCT is associated with young age of both the recipient and donor and normal liver histology in the recipient at transplantation [14, 15]. Mild liver involvement has been arrested by early HSCT, whereas advanced disease may warrant combined liver and bone marrow transplant [16].

C. parvum is a highly infectious protozoan parasite responsible for cryptosporidiosis in humans. Immunocompetent patients experience transient diarrhoea, while life-threatening infections can develop in immunocompromised patients with primary immunodeficiencies or HIV. *C. parvum* is a particularly important pathogen in individuals with CD40L deficiency since CD40 (the ligand of the CD40L gene) is expressed on bile duct epithelial cells and is a protein to which cryptosporidia can attach. Failure to clear the organism by means of T cell activation and resulting apoptosis of infected bile duct epithelial cells results in chronic infection [17, 18].

Currently effective anticryptosporidial drugs are not available although paromomycin appears to have modest activity against *C. parvum* and has benefited some patients with AIDS [19, 20]. A Cochrane review confirmed the lack of evidence for effective agents in immunocompetent or HIV-infected individuals, but no CD40L-deficient patients were included in the trials reviewed. These authors indicated that, as nitazoxanide reduces the load of parasites, this should be considered in immunocompromised patients [21], which should include immunodeficient as well as HIV-infected patients. Since there is no evidence relating to CD40L-deficient patients, a combination of drugs such as paromomycin, nitazoxanide, and azithromycin should be used in an attempt to suppress infection prior to consideration for HSCT [22].

Our case highlights that patients with CD40L deficiency who develop diarrhoea and abnormal LFTs should be considered as being at increased risk for cholangitis or malignancy regardless of their age [6] since cryptosporidia can cause morbidity and mortality at any age. Cholangiocarcinoma is a rare complication of CD40L defi-

ciency, which has been reported in boys with CD40L deficiency and individuals with AIDS [23]. Indeed there has been a report of a 38-year-old HIV-positive man who had cholangiocarcinoma 3 years after a diagnosis of AIDS-related cholangiopathy [24]. However, to our knowledge cholangiocarcinoma has not previously been reported in an adult with CD40L deficiency.

Other learning points include the diagnostic method of *C. parvum*. The organism is very difficult to detect during asymptomatic periods and immunofluorescence-based procedures, along with polymerase chain reaction, are more sensitive than stool microscopy for detecting *Cryptosporidium* in patients with immunodeficiencies [7] and should always be used.

Also early detection of complications of *C. parvum* infection is essential as there is good evidence that treatment and cure of resistant *C. parvum* infection can be achieved by BMT [14; de la Monte, pers. commun.]. Dimicoli et al. [4] described two brothers with CD40L deficiency affected with *C. parvum* infection and cholangitis. After BMT, expression of CD40L on activated T lymphocytes was normal and both *C. parvum* infection and cholangitis resolved [4]. However, in one study of CD40L deficiency in children with pre-existing liver disease, 5 out of 12 patients were found to be chronically colonised though only 1 had a known history of infection. Early testing is essential as HSCT is the best treatment for all uninfected children and should at least be considered early for surviving adults with CD40L deficiency [7].

Our patient was diagnosed with CD40L deficiency in early life and remained reasonably well until the age of 43 years. Survival to the fourth decade has been reported to be 50%, but the number of cases available for analysis in over 30 year olds is very small [22]. In this case, T254M

mutation was identified and has been associated with a milder disease course [25, 26] and those patients with this mutation were not reported to have liver disease or opportunistic infections. Our report sustains the opposite view in terms of liver disease, although our patient had one confirmed and one probable opportunistic infection [27, 28]. Not surprisingly, as in other primary immunodeficiency diseases, there is no genotype-phenotype correlation. Numerous mutations have been described in the disease and it is not possible to predict which patients will survive into adulthood [29]. Furthermore, there are likely to be several disease-modifying genes in addition to other possible disease-causing mutations or polymorphisms [27].

In conclusion we present an adult patient with CD40L deficiency who suffered the rare complication of cholangiocarcinoma arising from sclerosing cholangitis associated with chronic cryptosporidial infection that became apparent at a relatively late age. Diarrhoea, however mild or intermittent, or abnormal liver function tests should now be fully investigated in all patients with CD40L deficiency at an early stage, since the only successful therapy for this complication is HSCT, which is more likely to have a good outcome if done before the age of 15 years.

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