Colorectal cancer in patients with X-linked agammaglobulinaemia

JOS W. M. VAN DER MEER  RON S. WEENING
PETER T. A. SCHELLEKENS
IVO P. VAN MUNSTER
FOKKO M. NAGENGAST

Primary immunodeficiency disorders can predispose to certain malignancies but hitherto no such relation has been established for X-linked agammaglobulinemia (XLA). We have diagnosed rapidly progressive colorectal cancer in 3 unrelated young adults with XLA. We could find no explanation for the tumours. Since the calculated incidence of rectosigmoid cancer is increased 30-fold in patients with XLA, we advise the screening of these individuals, and perhaps people with other agammaglobulinemias, for colorectal cancer.


Gastrointestinal ailments are common in patients with primary agammaglobulinemia. Intestinal infections with Giardia lamblia, Campylobacter jejuni, and Salmonella spp are frequent. Gastritis with C jejuni infection may result in recurrent fever. In late-onset agammaglobulinemia (LOA), lymphonodular hyperplasia is common; the aetiology and pathogenesis of this abnormality are not known. Antral gastritis with abnormal gastrin production capacity is also a common finding in people with LOA, whose risk of developing gastric cancer is some 47-fold greater than that of the normal population. Malignant lymphoma is also 30 times more common in people with LOA. An increased risk of developing cancer is less well established for the other common types of agammaglobulinemia (X-linked [XLA] and early-onset agammaglobulinemia). Here we describe 3 unrelated patients with XLA who developed colorectal cancer at an early age.

Patient A was born in 1959 and agammaglobulinemia was diagnosed at an early age. Our diagnosis of XLA was based on family history, absence of B lymphocytes, and very low serum concentrations of immunoglobulins (IgG 0-6 g/L, IgA and IgM not detectable). 3 brothers with the same disorder had died of pulmonary complications, and an affected male cousin survives. There was no family history of colorectal or other cancers. The patient did well on intramuscular gammaglobulin until October, 1984, when he complained of abdominal distension, cramps, and diarrhoea. During the next few months he lost 16 kg and he was cachectic when admitted to hospital in March, 1985. He was pale with a pulse rate of 100/min, but there were no other abnormalities on physical examination. He had a haemoglobin concentration of 6·9 mmol/L, microcytic red blood cells, serum iron concentration of 1 mmol/L, and thrombocytosis (760 x 109/L). Serum albumin and IgG were 30 g/L and 1·3 g/L, respectively. A jejunal biopsy revealed complete villus atrophy, but no G lamblia infection. 2 weeks after admission an acute abdomen with hyperperistalsis developed. An abnormal mass was palpated on rectal examination. Subphrenic gas was seen on a chest radiograph. At laparotomy, a nonresectable rectal carcinoma was found together with a perforation and carcinomatous peritonitis. An adenocarcinoma was
diagnosed. The patient died a week later. Necropsy confirmed widespread metastatic rectal carcinoma.

**Patient B** was born in 1961 into a large family with a pattern of X-linked inheritance of agammaglobulinaemia (pedigree 66-8 in refs 10 and 11), but no history of colorectal cancer. There was almost no immunoglobulin in his blood and B lymphocytes were undetectable. He had bronchitis, recurrent bacteremia, and skin lesions due to *C jejuni*, and had slight cirrhosis of the liver after hepatitis B infection. The *C jejuni* infection had been cured with imipenem and plasma infusions. In December, 1990, diarrhoea occurred, for which no causative microorganism could be found. 7 months later, the patient was admitted with abdominal cramps, persistent diarrhoea, and weight loss. He had seen blood in his stools. Physical examination was unremarkable apart from a palpable mass on rectal examination.

The haemoglobin concentration was 7.7 mmol/L. Barium enema and sigmoidoscopy revealed a constricting rectal tumor 8 cm from the anal ring surrounded by multiple adenomas (0.5–2 cm diameter). Histology was consistent with adenocarcinoma. The tumour was resected but a metastasis was found in the liver. Despite chemotherapy, the cancer progressed rapidly and the patient died in December, 1991. Necropsy was not done.

**Patient C** is a 36-year-old man, diagnosed as having XLA on grounds of absent B lymphocytes and genetic studies (pedigree B2 in refs 10 and 11). 2 of his 3 brothers with XLA have died of pulmonary complications. There was no family history of colorectal or other cancers. Recurrent infection of the respiratory tract had led to mild bronchiectasis. The patient also had recurrent prostatitis and epididymitis, for which he had had an epididymectomy. His current illness started in May, 1992, with diarrhoea and abdominal cramps. At first these symptoms were attributed to antimicrobial therapy for a respiratory infection. He had seen traces of blood in his stools, which were found to contain *C jejuni*. On rectal examination, there was a palpable mass, which on histological examination proved to be an adenocarcinoma. In addition, a small adenomatous polyp was found in the rectum. At laparotomy, a massive nonresectable tumour was found infiltrating the adjacent structures.

Were these cancers coincidental or were they the result of XLA? There has been a report of multiple colorectal neoplasms in a 22-year-old man with congenital hypogammaglobulinaemia. Kinlen et al* found 2 patients with XLA and colon cancer in their survey of cancer in patients with hypogammaglobulinaemia. The registry of the Dutch Working Party for Primary Immunodeficiency has enrolled 52 X-linked agammaglobulinaemia patients, since no other cases of rectal or colonic cancer have been found so far in this group, the observed risk is 3/52 with a mortality of 2/52. The expected number of patients with rectosigmoid cancer and the expected number of deaths from this type of cancer can be calculated from data of the Netherlands Cancer Registry by multiplying the 5-year age-specific incidence and mortality rates for men by the corresponding person-years at risk. Incidence of rectosigmoid cancer for people with XLA is therefore 30-fold and mortality 59-fold greater than that of the normal population.

We are now seeing the first generation of patients with XLA who reach adulthood. This may be why an increased risk of cancer of the large bowel has not been noted previously. Patients with other types of agammaglobulinaemia might also be at risk, although other workers* did not find any such cancer in more than 220 patients with LOA.

**What pathogenetic mechanisms could underlie the development of these cancers?** Cellular immunity in XLA is normal, but the absence of a functional mucosal-humoral immune system might lead to alterations in intestinal microflora. Increased susceptibility to any pathogens present in the gut may lead to chronic inflammation and dysplasia. Multiple courses of antibiotics might further modify the microflora, especially those organisms producing potentially carcinogenic substances. Intimate contact between these substances and the bowel epithelium would be possible, owing to the deficiency in mucosal immunoglobulins. The patient reported by Adachi et al* had 20 adenomatous polyps and 9 adenocarcinomas in his colon. Histological examination of the resected bowel of patient B also showed multiple foci of adenomatoses. Therefore, there may be increased susceptibility to colorectal cancer. Long-term abdominal symptoms or irregular bowel movements should not be dismissed as the benign gastrointestinal ailments to which patients with XLA are prone. Infection with an enteric pathogen such as *C jejuni* may not be wholly responsible, and a more extensive diagnostic approach (endoscopic examination or barium enema) is indicated.

We thank Prof B. J. M. Zegers and other members of the Dutch Working Party for Primary Immunodeficiency for providing us with data on patients with XLA, and Dr E. J. B. M. Mensink and Dr J. P. Donnelly for their help.

**REFERENCES**


