The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/14883

Please be advised that this information was generated on 2019-10-28 and may be subject to change.
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 agammaglobulinaemia (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 agammaglobulinaemias, for colorectal cancer.

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 B2 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 bacteraemia, and skin lesions due to \textit{C jejuni}, and had slight cirrhosis of the liver after hepatitis B infection. The \textit{C jejuni} infection had been cured with imipenem and plasma infusions. In December, 1990, diarrhoea occurred, for which no causative microorganism could be found. Seven 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. 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 \textit{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 underly the development of these cancers? Cellular immunity in XLA is normal, but the absence of a functional mucosal-humoral immune system may 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 those 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 adenomatosis. 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 \textit{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