Monozygotic Twin Brothers with Primary Immunodeficiency Presenting with Metastatic Adenocarcinoma of Unknown Primary

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Acta Oncologica Vol. 37, No. 7/8, pp. 771–772, 1998

Received 3 April 1998
Accepted 8 July 1998

Primary immunodeficiency disorders (PID) appear to predispose patients to certain malignancies (1). The present report describes monozygotic twin brothers with X-linked hyper IgM syndrome (HIM) presenting with a metastatic adenocarcinoma of unknown primary. HIM is a rare disorder caused by mutation of the CD40 ligand gene. Consequently, no functional CD40 ligand is expressed on the surface of activated T cells. The significance of this case report lies in the identical clinical course of two genetically identical twins, emphasizing the unique susceptibility to malignancy in a given PID. To our knowledge, malignancy in association with PID has not been reported in another set of twins.

Case report. The brothers were diagnosed with HIM shortly after birth and later shown to have genetically identical mutations in the CD40 ligand gene (2). They received intravenous immunoglobulin every 3–4 weeks for the last 13 years of their lives and remained free of serious infections. They lived in the same environment throughout their lives.

In September 1993, at the age of 21, one of the brothers presented with a 4-week history of buttock pain, loss of erection, constipation, voiding difficulties and decreased sensation in the left thigh, anal and scrotal area. On examination, he had normal motor function but decreased light touch and pinprick sensation in the distribution of the left S3-5 dermatomes. MRI of the pelvis revealed a 10 cm lobulated mass to the left side of the sacrum and an abdominal ultrasound showed widespread liver lesions consistent with metastases, epigastric lymphadenopathy, and biliary duct dilation. Liver biopsy revealed a poorly differentiated adenocarcinoma. Immunohistochemistry of the liver biopsy was positive for keratin and focally positive for CEA, but negative for vimentin, prostatic acid phosphatase, chromagranin and placental alkaline posphatase, thus excluding germ cell tumor, melanoma and lymphoma. Investigations including upper and lower endoscopy, imaging of the spine, bone, chest and testes as well as tumor markers failed to reveal a primary malignancy. Treatment with a cisplatin-based chemotherapy protocol resulted in a partial response by September 1994. As the liver was the only known site of residual disease, hepatic resection of the lesions was attempted. Intra-operatively, peritoneal nodules were noted along with intra-abdominal lymphadenopathy, and therefore resection was not performed. Biopsies of a sigmoid peritoneal nodule revealed moderately differentiated adenocarcinoma. Despite further chemotherapy, the cancer progressed and he died in March 1995, 18 months after his diagnosis. An autopsy was not performed.

Screening for cancer of the patient's twin brother was undertaken. An abdominal ultrasound in September 1993 showed mild dilation of the intra- and extrahepatic bile ducts with no obvious etiology. A CT scan in May 1995 revealed a mildly enlarged spleen, thought to be compatible with HIM, and continued dilation of the bile ducts. Monthly liver function tests were normal until September 1995. Gastroscopy in September 1995 was normal. In October 1995, at the age of 23, he presented with abdominal pain and jaundice. CT scan revealed massive hepatomegaly and innumerable intrahepatic lesions consistent with metastases. Fine needle aspiration biopsy revealed a poorly differentiated adenocarcinoma. Despite an initial subjective improvement and a partial objective response to combination chemotherapy, he progressed with bone metastases. He was treated palliatively and died in May 1996, 7 months after his diagnosis. An autopsy was not performed.

Discussion. There are several types of PID, including ataxia telangectasia, common variable immunodeficiency, severe combined immunodeficiency, and HIM. Kinlen et al. (3) reported on 316 patients with a variety of PID diagnosed between 1957 and 1975. Eighteen patients in this cohort developed malignancy, for an incidence of 5.7%. In an age- and sex-matched population, this represents a relative risk (RR) of 6.0, largely due to an excess of stomach cancer (RR 50), lymphoma (RR 23) and cervical cancer (RR 13). This also represented a 6-fold increase in cancer mortality. For specific PID, published lifetime risks for tumor development have been estimated in the range of 12–25% (1).

A cancer registry of patients with PID has been developed at the University of Minnesota. Data on 500 cases, identified through literature review and voluntary reports, have been published (1) which further detail the type of cancers these patients develop, including Hodgkin's lymphomas, comprising 50.4% of cases, followed by leukemia in 12.6%, adenocarcinoma in 9.2%, Hodgkin's disease in 8.6% and other tumors in 19.2%. This distribution of cancer is different from the usual tumors seen in this young age group. In this registry, nearly half of the patients were diagnosed with their tumors before 10 years of age, although the patients reported by Kinlen et al. appeared to be older (3, 4). In the registry, 16 patients with HIM were reported to have malignancies, none with adenocarcinomas.

 ISSN 0284-186X

A recent case series reported specifically on malignancies in 9 patients with HIM and included the 2 patients in this report (5). The malignancies reported included carcinomas and carcinoid tumors, which were felt to develop from the biliary tree or associated structures and were often preceded by cholangitis or cirrhosis. The patients described here did not have pre-existing hepatobiliary disease, and it is the current authors' opinion that the primary site and cause is still unknown.

The increased risk of developing malignancies in primary immunodeficiency disorders is likely multifactorial, as it is with acquired immunodeficiency disorders. Possibilities include local factors such as achlorhydria, oncogenic viruses, chronic antigenic stimulation from repeated infections, immune surveillance abnormalities and/or immune regulation impairment (6). The occurrence of identical malignancies developing at about the same age makes one speculate that a shared pathogenetic abnormality existed and that a genetic clock was set at birth in these monozygotic twins.

REFERENCES

1. Filipovich AH, Mathur A, Kamat D, Kersey JH, Shapiro RS. Lymphoproliferative disorders and other tumors complicating immunodeficiencies. Immunodeficiency 1994; 5: 91–112.
2. Pabst HF, Chung SH, Segal D, Dolen J. Mild combined immunodeficiency in identical twins. J Pediatr 1976; 89: 425–8.
3. Kinlen LJ, Webster ADB, Bird AG, et al. Prospective study of cancer in patients with hypogammaglobulinemia. Lancet 1985; 2: 263–6.
4. Filipovich AH, Heinitz KJ, Robinson LL, Frizzera G. The Immunodeficiency Center Registry: a research resource. Am J Ped Hem/Oncol 1987; 9: 183–4.
5. Hayward AR, Levy J, Facchetti F, et al. Cholangiopathy and tumors of the pancreas, liver and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J Immunology 1997: 977–83.
6. Penn I. Why do immunosuppressed patients develop cancer? Crit Rev Oncog 1989; 1: 27–52.