Transitional cell carcinoma in a patient with X-linked hyperimmunoglobulin M syndrome

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Abstract

Patients with X-linked hyperimmunoglobulin M syndrome (XHIGM) have a defective CD40–CD40 ligand system and further immunoglobulin class-switching. They may present with recurrent infection and malignancy involving the liver, pancreas or biliary tract. We report here a case of poorly differentiated transitional cell carcinoma in a young man with XHIGM even on regular treatment and discuss the possible pathogenesis. Given that the triggering of the CD40–CD40 ligand system has been found to improve tumor immunogenicity in recent studies, future immunotherapy targeting the CD40 ligand for these patients may be feasible to prolong their survival.

Key words CD40 ligand, malignancy, transitional cell carcinoma, X-linked hyper-IgM syndrome.

X-linked hyperimmunoglobulin M syndrome (XHIGM) is a heterogeneous disease that is characterized by a mutation of the CD40/CD40 ligand signaling pathway, leading to defects in class-switch recombination. The CD40 ligand gene is located at Xq26.3-Xq27.1. Determination of a mutation of the CD40 ligand helps to diagnose XHIGM. This disorder is clinically manifested by low or absent serum IgG, IgA and IgE, with normal or elevated IgM. Affected patients may present with recurrent infection, malignancy and gastrointestinal tract problems such as diarrhea, oral ulcers and sclerosing cholangitis. To date, the most commonly reported malignancies include those that involve the liver, pancreas or biliary tract; there has been no prior report of urothelial cancer.

Case report

A 25-year-old man with the diagnosis of XHIGM presented with gross hematuria. Intractable diarrhea, failure to thrive, pneumonia, Candida infection of the oral cavity and esophagus led to the suspicion of immunodeficiency when the patient was 3 years old. Laboratory tests indicated low IgG and IgA, elevated IgM, normal neutrophil function and negative delayed-type hypersensitivity skin test (Table 1). Hyper-IgM syndrome was suspected. Regular i.v. immunoglobulin (IVIG; 500–800 mg/kg per month) and prophylactic antibiotics with sulfamethoxazole-trimethoprim were given. Despite IVIG treatment, the patient continued to have infections including pneumonia, salmonellosis, cryptococcal meningitis, herpetic gingivostomatitis, staphylococcal neck abscess and recurrent cholecystitis. Sclerosing cholangitis was diagnosed on liver biopsy at 24 years of age. After discussion with the patient’s family, blood sample was sent for genetics analysis after informed consent was obtained. A mutation was detected, in which tyrosine 169 was replaced by asparagine (t526a) on exon 5 of the CD40 ligand gene. This finding is consistent with the diagnosis of the X-linked hyper-IgM syndrome.

The patient was then admitted for further examination. A renal ultrasound showed the right kidney with pelvicicestsisis, and a relatively large left kidney. I.v. urography poorly visualized the left pelvocalyceal system. Abdominal computed tomography (CT) showed a left renal tumor in the middle pole with renal vein thrombosis and metastatic lymphadenopathy in the left paraaortic region (Fig. 1). Chest X-ray showed multiple nodules diffusely scattered in both lungs with the left pleural effusion. In addition, a mass in the left testis, 11 × 9 mm in size, was noted with left inguinal lymphadenopathy. Germ cell tumor or poorly differentiated transitional cell carcinoma (TCC) were considered at first, but blood β-human chorionic gonadotropin was 57.27 mIU/mL and α-fetoprotein was <2.76 ng/dL. Both tumor markers for germ cell tumors were within normal limits. The other laboratory results are listed in Table 2. CT-guided renal biopsy, ultrasound-guided thoracocentesis and left orchietomy confirmed poorly differentiated TCC (Fig. 2), which was staged as T3N2M1 according to the Union for International Cancer Control and American Joint Committee on Cancer (http://www.cancer.gov/cancertopics/pdq/treatment/transitionalcell/HealthProfessional/page3).

Due to his young age and unstable condition, chemotherapy with etoposide, cisplatin and bleomycin (BEP) was started after consulting the oncologist under the initial suspicion of germ cell tumor. In men with good-prognosis metastatic germ cell tumor, the standard three-cycle BEP chemotherapy regimen is associated with a high survival rate. Unfortunately, the present course was complicated by persistent fever, neutropenia and hypotension. Broad-spectrum antibiotics including teicoplanin,
meropenem and fluconazole, IVIG (800 mg/kg) and granulocyte colony-stimulating factor were used to treat suspected septic shock, but the patient continued to deteriorate and died 11 days after initiation of chemotherapy.

Discussion

The present XHIGM patient developed TCC at 25 years of age, which is younger than most patients previously reported with urothelial cancer. Although it cannot be definitively proven that XHIGM was responsible, there is some evidence to suggest that defective CD40 ligation is associated with oncogenesis.

The CD40–CD40 ligand interaction is an essential signal for B-cell proliferation, formation of B memory cells and germinal center, immunoglobulin production and isotype switching. Hyper-IgM syndrome is a rare immunodeficiency disorder caused by a heterogeneous defect in the CD40/CD40 ligand signaling pathway. XHIGM results from defects in the CD40 ligand gene, which produces the CD40 ligand: a T-cell surface molecule. The genetic defect of activation-induced cytidine deaminase (AID) in B cells causes the autosomal recessive hyper-IgM syndrome. Children with X-linked hyper-IgM and hypohydrotic ectodermal dysplasia (HIM-ED) have a mutation in the IκB kinase-γ (IKK-γ) gene, also known as NF-κB essential modulator (NEMO). All patients with the hyper-IgM syndrome develop low serum immunoglobulin levels and recurrent respiratory tract infections. Patients with XHIGM, however, caused by genetic defects in the CD40 ligand, are especially susceptible to opportunistic infection, gastrointestinal disease and malignancy. These findings suggest that T-cell immunity is also affected in patients with XHIGM. Defective CD40–CD40 ligand interaction, involved in the development of certain autoimmune diseases

Table 1  Immunological profile

|            | 3 years | 19 years† | 23 years† |
|------------|---------|-----------|-----------|
| IgG (mg/dL)| 12      | 429       | 598       |
| IgA (mg/dL)| <6      | 10        | 7         |
| IgM (mg/dL)| 104     | 66        | 224       |
| IgE (IU/mL)| <20     | 1         | 1         |
| CD3 (%)    | 43      | 45.3      | 65.5      |
| CD4 (%)    | 12      | 24.9      | 38.5      |
| CD8 (%)    | 22      | 17.4      | 21.0      |
| CD19 (%)   | 40      | 41.1      | 19.3      |
| CD57 (%)   | –       | 2.5       | 4.1       |
| Active T cell (%) | –       | 8.4       | 8.3       |
| CH50 (IU/mL)| –      | 45        | –         |

†IVIG treatment. Normal range: IgG, 639–1349 mg/dL; IgA, 70–312 mg/dL; IgM, 24–89 mg/dL; IgE, 1.53–114 mg/dL; CD3, 55–83%; CD4, 28–57%; CD8, 10–39%; CD19, 6–19%. CH50, common pathway hemolytic titer-50%.

Table 2  Other laboratory tests

|                      | Biopsy day | Before chemotherapy | Death |
|----------------------|------------|---------------------|-------|
| WBC count (/μL)      | 5700       | 9500                | 200   |
| Absolute neutrophil count (/μL) | –         | 4845                | 0     |
| Hemoglobin (g/dL)    | 12.0       | 10.4                | 6.5   |
| Platelet (/μL)       | 539 000    | 529 000             | 103 000 |
| CRP (mg/dL)          | –          | 34.8                | 31.6  |
| AST (IU/L)           | 68         | 89                  | 58    |
| ALT (IU/L)           | 74         | 65                  | 55    |
| Total bilirubin (mg/dL) | 4.3    | 5.7                 | 18.4  |
| Direct bilirubin (mg/dL) | 2.3   | 4.0                 | 10.2  |
| BUN (mg/dL)          | 24         | 29                  | 37    |
| Creatine (mg/dL)     | 1.7        | 1.9                 | 2.4   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; WBC, white blood cell.

Fig. 1  (a) Abdominal computed tomography (CT) showing left renal tumor in the middle pole (arrow) and metastatic lymphadenopathy in the left para-aortic region (arrowhead). (b) Chest X-ray showing multiple scattered nodules in the bilateral lung field and left-sided pleural effusion.
Hussain et al evaluated with both a lower stage and a lower grade. It is not unique, found that the CD40-positive tumors were significantly associated with a poor prognosis in patients with TCC. In addition, a defect of the CD40 or CD40 ligand has been shown in infection occurred over a long time before the cancer developed. It is possible, however, that such infection. It is possible, however, that.

In contrast, tumors of the renal pelvis usually occur after middle age. The peak age is the seventh decade. The risk factors associated with the development of urothelial cancer include cigarette smoking, exposure to aniline dyes and Schistosoma haematobium. Infection with this parasite increases the incidence of both TCC and squamous cell carcinoma in many developing countries. In the present patient, the tumor biopsy showed no evidence of TCC and squamous carcinoma in the gastrointestinal tract. Carcinoma of the liver, pancreas, duodenum and biliary tree may cause death: the prevalence has been reported as 3.57%, 4% and 17% respectively in different studies. The pathogenesis of this disorder remains unclear. Viral hepatitis, such as the hepatitis B virus, eventually causes liver cirrhosis and hepatocellular carcinoma. Infection of the biliary tract with Cryptosporidium parvum also predisposes patients to the possibility of developing sclerosing cholangitis and tumors of the liver, pancreas and biliary tract.

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The present patient had a missense mutation at nucleotide 526 from T to A, which caused tyrosine at location 169 to be replaced by asparagine. This mutation was located on exon 5, the tumor necrosis factor (TNF) domain. Pilot studies have shown that the TNF superfamily modulates immune cell survival. CD40 ligation following T-cell activation via T-cell receptor/CD3 complex interaction with the co-stimulatory B7/CD28 signal, could induce cell apoptosis. Patients with XHIGM have a defect in the CD40 ligand gene, which causes not only poor B-cell differentiation, but also impaired function of NK cells, monocytes, dendritic cells and T cells. That might explain why patients with mutated CD40 ligand lose the tumoricidal ability.

Prior in vivo and in vitro studies have shown that CD40 ligation can induce tumor cell apoptosis. Hirano et al. used a recombinant soluble human CD40 ligand both to inhibit the proliferation of the CD40-bearing human breast cancer cell lines and increase the survival of tumor-bearing mice. Posner et al. found that the tumor cell growth of certain CD40-expressed squamous cell carcinomas of the head and neck was downregulated by trimeric CD40 ligand. In ovarian carcinoma cells, Koppold et al. showed that efficient gene transfer of CD40 ligand might activate dendritic cells and the immune response, such as expression of interleukin-12. These studies suggested that the CD40 ligand may be a potential anti-tumor agent. Bugajska et al. used the soluble trimeric CD40 ligand to inhibit growth of normal and malignant urothelial cells. Only the cell surface-presented CD40 ligand, however, could induce massive apoptosis in CD40-positive TCC cells.

**Conclusion**

The present XHIGM patient developed TCC during the third decade of life. Regular IVIG treatment reduces the frequency and severity of infections in these patients, but it has no effect on the frequency of lymphoproliferative disease, sclerosing cholangitis or the development of malignancies. XHIGM can be cured only with bone marrow transplant. Recent studies have also shown that CD40 ligand immunotherapy, delivery by attenuated Salmonella typhimurium or adenovirus, has therapeutic effects on hematologic malignancies and some solid tumors in mice. Furthermore, s.c. recombinant CD40 ligand in three children with XHIGM resulted in positive delayed-type hypersensitivity reaction, restored T-helper cell function, and synthesis of effector cytokines during the treatment period. This raises the possibility of future amplification of this ligand in patients with XHIGM, which may reduce both the risk of developing infection, and malignancy.

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Successful treatment of relapsing autoimmune thrombotic thrombocytopenic purpura with rituximab

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening condition characterized by thrombotic microangiopathy. The standard treatment for TTP is plasmapheresis. For refractory or relapsing cases, various immunosuppressive agents have been tried, and among them rituximab has shown promising results. TTP is rarer in the pediatric age group and the use of rituximab in children with TTP is limited. Reported herein is the successful treatment of relapsing autoimmune TTP with rituximab in a 12-year-old girl.

Key words ADAMTS13 deficiency, plasma exchange, plasmapheresis, relapse, rituximab, thrombocytopenia, thrombotic thrombocytopenic purpura.

Thrombotic thrombocytopenic purpura (TTP) is a rare medical emergency characterized by the presence of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia.1,2 TTP occurs primarily in adults and features thrombotic microangiopathy.3 Prompt recognition is required given that this condition responds well to plasmapheresis. In this report, we describe a girl with TTP who relapsed with plasmapheresis and subsequently responded well to rituximab.

Case report

A 12-year-old girl was admitted with a 2 week history of headache and a 1 week history of neck pain. One week before the admission, she was seen by her primary care physician, who diagnosed a viral infection and advised ibuprofen. Her symptoms worsened and 2 days before presenting to us, she developed decreased appetite, intermittent fever (maximum temperature, 38.8°C) and three episodes of non-bilious vomiting. On the day of admission, she developed a transient episode of epistaxis and presented at an outside hospital. She was noted to have petechiae, and complete blood count (CBC) indicated low platelet count and anemia. A diagnosis of Evan’s syndrome/immune thrombocytopenic purpura (ITP) was considered at the outside hospital and she was referred to University Health (affiliated to Louisiana State University Health Sciences Center, Shreveport) for further management.

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