Case Report

Intractable colitis associated with chronic granulomatous disease

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The case of a 20-year-old Japanese man, diagnosed as having autosomal recessive chronic granulomatous disease (CGD), who was being treated with corticosteroids for intractable unclassified colitis, is described. He died from multiple organ failure following disseminated intravascular coagulation secondary to disseminated varicella-zoster virus (VZV) infection. He was diagnosed as an index case of CGD when 2 years old, was inoculated against VZV at the age of 5 years and had had an unremarkable course for 19 years. He was admitted to hospital because of a third episode of recurrent bloody diarrhoea. Clinical remission for each episode was achieved by intravenous corticosteroid therapy. Unclassified colitis associated with CGD was diagnosed based on a colonic biopsy demonstrating characteristic macrophages with lipofuscin deposits. From a treatment viewpoint, idiopathic inflammatory bowel disease (IBD) should be differentiated from secondary IBD occurring in CGD, in which immunosuppressive drugs including corticosteroids, still the mainstay of IBD treatment, should be avoided.

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Introduction

Chronic granulomatous disease (CGD) is an X-linked (approx. 65 % of CGD patients result from defects in *gp91^{phox}*) or an autosomal recessive [the remainder are due to defects in *p47^{phox}* (30 %), *p67^{phox}* (<5 %) or *p22^{phox}* (<5 %)] disorder typified by a defect of phagocytic respiratory bursts (Winkelstein *et al.*, 2000). Gastro-intestinal (GI) manifestations, including gastric outlet obstruction and colitis, occur in up to 25–50 % of CGD patients (Schäppi *et al.*, 2003). The prevalence and severity of GI involvement in X-linked patients has been reported to be significantly higher than in autosomal recessive patients. In a recent report on a cohort of 140 patients with CGD, all 46 patients with GI involvement had abdominal pain and were dependent on treatment with corticosteroids. However, 71 % relapsed after discontinuation of corticosteroids and required retreatment (Marciano *et al.*, 2004).

Varicella-zoster virus (VZV) is now recognized as one of eight herpesviruses that infect humans. Varicella (chicken-pox) represents primary infection with VZV, while zoster (shingles) results from reactivation of latent virus. An association between corticosteroid use and severe varicella has been recognized for decades, although most reports have come from relatively small retrospective series and case

reports (Dowell & Bresee, 1993). The largest, albeit retrospective, study to date of varicella in children with acute lymphoblastic leukaemia reported by Hill *et al.* (2005) provides convincing evidence that prednisone therapy during the VZV incubation period significantly increases the risk of developing severe varicella infection. In addition, an older age is associated with more severe infection.

We describe a CGD patient with severe colitis who was treated with corticosteroids and eventually developed a lethal disseminated varicella infection. We also describe genome analysis of VZV from this patient.

Case report

A 20-year-old Japanese man was admitted to our hospital because of recurrent bloody diarrhoea. When 2 years old he was diagnosed as an index case of CGD because of furunculosis, a negative nitroblue tetrazolium test, and an unremarkable family history. An autosomal recessive trait was suggested based on absence of a mutation of *gp91^{phox}*. Other gene states remain unknown. He had been inoculated against VZV at the age of 5 years, was receiving a prophylactic sulfamethoxazole–trimethoprim mixture and antimycotic drugs and his course had been uneventful until about a year before referral.

Bloody diarrhoea first began at the age of 19 years. Unclassified colitis associated with CGD was diagnosed

Abbreviations: CD, Crohn's disease; CGD, chronic granulomatous disease; GI, gastrointestinal; IBD, inflammatory bowel disease; UC, ulcerative colitis.

(Fig. 1), and pathological examination of colonic biopsies revealed characteristic pigmented macrophages with lipofuscin deposits (Fig. 1f) (Levine *et al.*, 2005). The bloody diarrhoea quickly resolved with intravenous prednisone (60 mg per day) infusion after failure of 5-aminosalicylate. Four months after the initial episode when oral prednisone was being tapered to 7.5 mg per day, his diarrhoea recurred, but remitted with 60 mg intravenous prednisone. It flared again during tapering of prednisone to 17.5 mg per day, and he was admitted to our hospital 6 months after the second relapse.

Fig. 1. Barium enema study (a), colonoscopic findings (b–e) and representative haematoxylin and eosin section of colonic biopsy specimens (f). (a) Diffusely damaged mucosa is seen along with a cuff-button ulcer in the proximal part of the descending colon; longitudinal ulcers are seen distally. (b) Yellowish white spot reflecting cryptitis or crypt abscesses; (c) indigo carmine dye spray reveals diffuse small dimpling. (d) Shallow geographic ulcers with inflamed intervening mucosa. (e) Deep discrete ulcers with cobblestone-like appearance. (f) Fine, granular, golden-brown to yellow pigmented macrophages with lipofuscin that do not stain for iron are indicated by red arrowheads.

He was having eight bloody diarrhoeas each day, but examination was unrevealing except for slight lower abdominal tenderness. Clinical remission was once again achieved with 40 mg intravenous prednisone per day for 2 weeks. On the 35th hospital day, while receiving 35 mg prednisone per day, he suddenly experienced severe back-ache and developed an atypical haemorrhagic vesiculopapular rash on his face and anterior chest. Broad-spectrum antibiotics were started immediately. Next day, because of progressive thrombocytopenia, disseminated intravascular coagulation (DIC) due to cryptogenic infection was strongly suspected and antifungal and antiviral (acyclovir) agents, gamma-globulin and gabexate mesilate were administered empirically. On the 37th day, severe DIC (platelet count $56\,000\ \mu\text{l}^{-1}$, fibrinogen $<50\ \text{mg dl}^{-1}$, FDP $>150\ \text{mg dl}^{-1}$) and liver dysfunction (AST $2228\ \text{IU l}^{-1}$ and ALT $1254\ \text{IU l}^{-1}$) ensued and lethal haemorrhagic shock developed.

Autopsy revealed that the immediate cause of death was multiple organ failure due to disseminated VZV infection. Intranuclear inclusion bodies or multinucleated giant cells suggesting VZV infection were detected in his colon, skin, oesophagus, liver, spleen, pancreas, adrenal glands and bone marrow. Severe liver dysfunction was caused by so-called varicella hepatitis. VZV genome analysis employing PCR-RFLP revealed a wild-type VZV infection (varicella) without reactivation of the latent vaccination strain (zoster) (Fig. 2).

Fig. 2. VZV genome analysis employing PCR-RFLP. Each amplicon of VZV genomic PCR was digested by *BssHIII* and *NaeI*. Lanes: 1, Oka vaccine strain; 2, wild-type strain; 3, size marker; 4, colonic DNA extracted from the patient. The digested band length from the wild-type strain is identical to that from the patient's DNA (upper arrow), and the lower arrow indicates the digested shorter band from the Oka vaccine strain.

Discussion

CGD patients are not susceptible to VZV infection but are susceptible to catalase-positive bacteria or fungal infections because the respiratory burst in phagocytes producing hydrogen peroxide is impaired and catalase-positive organisms are resistant to self-produced hydrogen peroxide. Therefore, this patient received life-long sulfamethoxazole-trimethoprim and antifungal chemoprophylaxis (Gallin *et al.*, 2003). Since prednisone therapy significantly increases the risk of severe varicella infection developing in children with acute lymphoblastic leukaemia (Hill *et al.*, 2005), there may be implications for other diseases that are treated with corticosteroids, in addition to CGD with colitis. Although our patient had been inoculated against VZV in his childhood, and the source of exposure could not be identified, VZV genome analysis revealed varicella with a wild-type strain (Fig. 2). This is not surprising because reinfection is well known to occur despite the presence of specific humoral and cell-mediated immunity to VZV at the time of exposure, provided the virus load is high enough to overwhelm immune defences (Martin *et al.*, 1994). Furthermore, several possible risk factors for the occurrence of varicella reinfections have been suggested: (1) age less than 12 months, (2) mild initial first infections and (3) genetic factors suggested by a familial occurrence of repeat varicella infections (Quinlivan & Breuer, 2006). The first two of these factors may be associated with a poor memory cell response, which is insufficient to confer protection against a second infection. Unfortunately, it remains unknown whether or not our patient had any of the risk factors mentioned. Because the wild-type strain is more virulent than the recurrent vaccine strain, and despite adequate treatment with acyclovir, death was probably inevitable in this patient given his background of immunocompromised status, CGD and high-dose corticosteroid therapy against intractable colitis.

Since CGD was first described, the colitis has been thought to be a variant of Crohn's colitis. In the present case, however, bloody diarrhoea was predominant among the symptoms of colitis, suggesting an association with ulcerative colitis (UC) rather than Crohn's disease (CD). There were also overlapping findings between UC and CD on the imaging studies undertaken (Fig. 1): the barium enema suggested fulminant UC rather than Crohn's colitis (Fig. 1a); and colonoscopic findings were characteristic of ulcerative colitis (Fig. 1b–d) with some features of CD (Fig. 1e). 'Indeterminate colitis' originally referred to 10–15% of cases of inflammatory bowel disease (IBD) in which there was initial difficulty in distinguishing between UC and CD in the colectomy specimen, but which usually evolved to either definite UC or CD on follow up. Pathological examination of colonic biopsy specimens revealed pigmented macrophages with lipofuscin deposits (Fig. 1f), which are reported to be highly suggestive of colitis associated with CGD (Levine *et al.*, 2005). Considering all the features, unclassified colitis associated with CGD should be diagnosed in this case.

Mutations of *NOD2/CARD15*, which functions as an intracellular pattern-recognition molecule against exogenous pathogens, have been reported to be associated with genetic susceptibility to CD (Hugot *et al.*, 2001). Disorders characterized by neutrophil dysfunction, such as CGD, glycogen storage disease 1B and Chédiak–Higashi syndrome, develop granulomatous colitis mimicking Crohn's colitis (Lekstrom-Himes & Gallin, 2005). Collectively, a possible link between defective innate immunity and colitis in the above diseases has misled us into treating the colitis along similar lines to CD, resulting in 5-aminosalicylate and corticosteroids becoming established as the first line treatment (Chin *et al.*, 1987). From our tragic experience, intractable unclassified colitis associated with CGD should be specifically treated, and immunosuppressive drugs including corticosteroids, which remain the mainstay of Crohn's treatment, should be avoided. In contrast, immunological restorative or potentiative strategies, such as granulocyte/macrophage colony stimulating factor (G/M-CSF) (Wang *et al.*, 2005), bone marrow transplantation (Güngör *et al.*, 2005) or gene therapy, should be more appropriate. Determination of the optimal treatment of colitis secondary to CGD is an urgent goal.

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