Epstein-Barr virus related lymphoma in inflammatory bowel disease

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Abstract

Epstein-Barr virus (EBV) induced lymphoproliferative disease is a well-known, feared complication of EBV primo-infection in children treated with immunomodulators or immunosuppressive drugs, eg after transplantation. As the incidence of inflammatory bowel disease (IBD) in young children is rising, more young EBV naïve patients are treated with immunomodulatory agents. It is not yet clear whether these patients carry the same risk as transplanted patients to develop lymphoproliferative disease and if so, whether their evolution is comparable. We present the history of a young patient with Crohn's disease who developed an EBV related lymphoma shortly after the primo-infection while being treated with azathioprine. This case argues for a rigorous follow up of young IBD patients treated with immune suppressive drugs, also regarding EBV status. (Acta gastroenterol. belg., **2008**, 71, **33-35**).

Abbreviations

PTLD : Post-transplantation lymphoproliferative disorder
EBV : Epstein-Barr virus
IBD : inflammatory bowel disease

Introduction

Recent publications draw the attention to a slight but significant increase of the incidence of lymphoma in patients with IBD (1,2). The use of immunomodulators seems associated with the increase in incidence of lymphoma (1,2). It is not clear whether this increase is correlated with disease severity or with the treatment itself (1,2). In these reviews, the possible role of EBV is not highlighted.

Post-transplantation lymphoproliferative disorder (PTLD) due to a primo Epstein-Barr virus (EBV) infection in children treated with immunosuppressive drugs is a well-known complication after transplantation. These patients are at risk for developing EBV related lymphoma (3).

As the incidence of inflammatory bowel disease (IBD) in young patients is rising, an increasing group of EBV naïve patients is treated with immunomodulators such as azathioprine or 5-mercaptopurine, which are associated with lymphoproliferative disease in the setting of solid organ transplantation. Therefore a close monitoring for the early detection of PTLD is proposed in transplant patients. This might also be adducible in paediatric IBD patients.

We present a boy with Crohn's disease, treated with azathioprine, who developed lymphoproliferative disease and consequently a fatal lymphoma after his primo-infection with EBV. This case report pleads for the same rigorous follow-up of the EBV status of these patients as is advised in transplanted patients.

Case report

At 14 years of age the patient presented with abdominal pain, fever, anal fissure and erythema nodosum. The diagnosis of Crohn's colitis was made by endoscopy with histology and he was treated with corticosteroids, mesalazine and metronidazole. A perianal abscess was present at time of diagnosis and drained. Initially his symptoms did not respond to the treatment and tube feeding with Modulen Nestlé® was associated, inducing a remission with possibility to stop steroid and metronidazole treatment. He was treated with mesalazine and Modulen Nestlé® (500 ml/ day) further on. His weight evolution and growth followed the 25th centile.

One year after diagnosis he had an exacerbation with anal and abdominal pain, anal blood loss, fever and fatigue accompanied by a painful anal ulceration without perianal inflammation. Introduction of metronidazole only temporarily improved his complaints.

The anal abscess was drained and azathioprine was associated at the age of 15. Due to leucopenia (2710/mm^3, 1220 neutrophils/mm^3) the daily dose was diminished from 1 mg/kg to 0.5 mg/kg. With this dose leucocytes normalised (5340/mm^3).

Eight months later he developed an EBV-hepatitis with fever, jaundice, generalised adenopathies and fatigue. A pancytopenia was present (leucocytes 640, thrombocytes 13000, RBC 2760000 /µL). Bone marrow aspiration demonstrating histiocytes with included RBC was suggestive for "macrophage activation syndrome" however, the ferritin level was low. The azathioprine was immediately stopped.

Large cervical adenopathies caused dysphagia and aspiration pneumonia complicated the clinical course. Because of infiltrates not responsive to antibiotics, a lung biopsy was performed. This was suggestive for

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EBV related lymphoproliferative disease, but sputum culture repeatedly revealed aspergillus fumigatus species. He was treated with caspofungine, aciclovir and steroids with only temporary effect on the adenopathies. Therapy with rituximab (an anti-CD20 antibody) initially led to a decrease in viral load and adenopathies. The clinical course was further complicated by several episodes of gastrointestinal bleeding, which were endoscopically treated.

He had persisting fever and the adenopathies reoccurred. The biopsy of a cervical adenopathy confirmed EBV related lymphoproliferative disease with arguments for development of a large cell lymphoma. In the meanwhile the pancytopenia persisted. Therapy with steroids, rituximab, vindesine and cyclofosfamide was initiated but had only limited impact on the process. Radiotherapy failed to reduce the volume of the adenopathy and the patient died 3 months after his initial EBV infection at the age of 16 years.

Discussion

PTLD is due to an EBV-induced B cell proliferation. An EBV-associated protein (LMP-1) engages host proteins from the tumor necrosis factor receptor family leading to cell growth and transformation. This is normally controlled by cytotoxic T-cell activity (4, 5). The presentation can be a localised or dissiminated lymphomatous disease. In the post-transplant setting overall immune suppression and EBV status are the major risk factors for PTLD (3,6). Because > 90% of the population has EBV immunity by the age of 40 (6), this type of complication will probably be observed in the paediatric and young adult cases as it was the case in solid organ transplantation (3).

Since the age of presentation of IBD is decreasing (7) and azathioprine is an important drug in controlling the disease, the number of EBV naïve patients with this type of immune suppression will increase. There is a slight increase in lymphoma risk in patients with IBD (1). It is however not clear whether this is the result of disease severity or immunomodulating therapy (1,2). Data on the proportion of EBV induced lymphoma in IBD are scarce. The first case of EBV-induced lymphoma was reported by Larvol *et al.* in 1994 (8). Although this type of lymphoma remains a rare complication in IBD we should have a high index of suspicion to detect them early. In a study reviewing all cases of lymphoma in patients with IBD, Dayharsh *et al.* reported 7 out of 18 to be EBV positive of which 6 were treated with azathioprine or mercaptopurine (9). Juffermans *et al.* described 3 patients with IBD developing EBV related lymphoma after respectively 1, 7 and 9 years of azathioprine. These adult patients responded to azathioprine withdrawal and treatment with rituximab (10). Questions arise whether the aggressive evolution in the described patient is a consequence of the low tolerance (0.5 mg/kg) to azathioprine in this patient.

Since azathioprine is an important therapeutic drug in IBD, there is a need for identification of IBD patients at risk of developing EBV related lymphoproliferative disease. EBV-DNA in plasma is used as a marker in patients at risk following solid organ transplantation. In patients with IBD the EBV viral load is similar to EBV-seropositive controls (11). However, some patients with refractory IBD have transient, very high EBV-DNA values (12). The long-term clinical outcome of these patients is not yet determined (9). At this moment, data are lacking to support systematic screening of IBD patients for EBV replication. Use of immunomodulators is an important cornerstone in the treatment of IBD, preventing relapse (12-15). Data on young patients treated with these agents should be collected prospectively, in order to ascertain their long-term safety. Further research is needed concerning the predictive value of EBV-DNA levels for the development of non-Hodgkin-lymphoma in these patients.

Conclusion

Since immunosuppressive drugs are an essential part of IBD therapy and IBD patients tend to present at younger age the identification of patients at risk of developing EBV-related lymphoproliferative disease is urgently needed.

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