Primary Sclerosing Cholangitis, Crohn's disease and HLA-B27 in Black South African Women

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Abstract

Crohn's disease is rare in South African black people and primary sclerosing cholangitis (PSC) is also rare in black patients with IBD, from South Africa. The presence of HLA-B27 is generally associated with seronegative spondylo-arthropathies and correlates with the occurrence of ankylosing spondylitis, recurrent mouth ulcers and uveitis, in patients with IBD. We describe two women with the combination of Crohn's disease, PSC and HLA-B27 from our cohort of the last 5 years of three black patients with Crohn's disease. Crohn's disease, PSC and HLA-B27 respectively, occur rarely in black South Africans and their concurrent presence in two black women suggests a pathogenetic link of HLA-B27 between Crohn's disease and PSC in this population. Female gender might be an additional determinant in this setting. (Acta gastroenterol. belg., **2012**, 75, **454-457**).

Key words : Crohn's, primary sclerosing cholangitis, HLA-B27, South Africa.

Introduction

Primary sclerosing cholangitis (PSC) is characterised by inflammation and progressive stricturing of the intra- and extra-hepatic biliary tree. Sixty to 80% of patients with PSC have concomitant inflammatory bowel disease (IBD). The associated IBD is ulcerative colitis (UC) in 80% and Crohn's disease in 20% of cases (1). A minority of patients with IBD, present with typical biochemical and histological features of PSC, but have normal cholangiograms. This is termed small-duct PSC (2). Small-duct PSC is the most common hepato-biliary condition associated with Crohn's disease (2). Although large series of inflammatory bowel disease (IBD) in the African American population have been published, Crohn's disease is rare in black people from South Africa (3,4). The Human Leukocyte Antigen, HLA-B27 is associated with spondylo-arthropathies and may be predictive of the occurrence of extra-intestinal manifestations in IBD, notably uveitis, recurrent mouth ulcers and ankylosing spondylitis (5,6). Although relatively rare in black African individuals from the sub-Saharan region, HLA-B27 has been documented in black patients from South Africa (7,8). We report on two black women with Crohn's disease and PSC, associated with the presence of HLA-B27.

Patients and Methods

Two black South African women with Crohn's disease were identified at the gastroenterology clinic of the Universitas Hospital in Bloemfontein, in the Free State province of South Africa, in 2009. Both were Sesotho first language speakers. Both were investigated for persistently raised cholestatic enzymes. We reviewed our records, to identify other black patients with Crohn's disease seen during the last five years. The liver histology of the two cases presented here, was reviewed by a senior pathologist (BDM) and magnetic resonance cholangiography (MRC) images were analysed by two senior radiologists (JJvanR and CSdeV). Colonoscopy was performed by a trained operator (OCB). Blood tests done as part of their routine work up were performed by the National Health Laboratory Service (NHLS).

The first patient, a 26 year old black woman from Bloemfontein, presented with chronic diarrhoea, abdominal and back pain. She was diagnosed with ulcerative colitis in 2003 and then already had elevated alkaline phosphatase (ALP) and γ-glutamyl transferase (γGT). On review in 2009, her disease was re-classified as Crohn's disease, based on the clinical, laboratory and colonoscopic findings. She had ulceration of her terminal ileum at endoscopy and colonic inflammation isolated to the ascending colon. The colon distal to this was endoscopically and histologically normal at the time. A CT scan showed thickening of the terminal ileum. Tuberculosis was meticulously excluded and she tested negative for the human immunodeficiency virus (HIV). She was found to be HLA-B27 positive, although no evidence of an axial arthropathy was found on magnetic resonance imaging (MRI) of the spine. Alkaline phosphatase and γGT remained elevated, and are given together with other relevant blood tests in Table 1.

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Submission date : 13/10/2011
Acceptance date : 26/02/2012

Table 1. — **Characteristics of the patients**

	Patient 1 Baseline (biopsy)	Under therapy (6 months)	Patient 2 Baseline (biopsy)	Under therapy (6 months)
Age (years)	26		44	
Gender	Female		Female	
Ethnic origin	Black African		Black African	
Language group	Sesotho		Sesotho	
ALP (40-120 U/L)	513	809	497	125
γGT (0-35 U/L)	666	835	300	82
Bilirubin (< 17 mol/L)	11	20	8	5
CRP (mg/L)	20.2	52	7.2	8.4
HLA-B27	Positive		Positive	
ANA	Negative		Negative	
SMA	Positive		Positive	
AMA	Negative		Negative	
c-ANCA	Positive		Positive	
p-ANCA	Negative		Positive	
Magnetic Resonance Cholangiography	Inconclusive		Inconclusive	
Liver histology	PSC		PSC	

Magnetic resonance cholangiography showed limited peri-portal T2 hyperintensity, indicative of inflammation. In the absence of other characteristics, PSC could not be conclusively diagnosed. A liver biopsy was performed. The liver biopsy showed lymphocytic infiltration of the portal tracts with damage to interlobular bile ducts, fibrous expansion of the portal tracts and focal interface changes. There was no evidence of bridging fibrosis or cirrhosis. These features were compatible with primary sclerosing cholangitis stage II (periportal stage) (9). During the course of the disease, she developed peripheral arthralgia, without arthritis and erythema nodosum. She was started on azathioprine 100 mg and ursodeoxycholic acid (UDCA) 15 mg/kg. Due to sequential intolerance to azathioprine, 6-mercaptopurine and methotrexate, a request has been forwarded to the clinical head of the institution to ask for authorisation of anti-TNF therapy and is pending.

The second patient was a 44 year old black woman, from Welkom in the Free State province of South Africa, with chronic diarrhoea, who had been on sulphasalazine since 2005 for a diagnosis of ulcerative colitis. She was seen with poorly controlled disease. Endoscopically she was found to have pan-colonic inflammation and ileitis. She had, had an ischiorectal abscess drained just before she was referred to us. Perineal examination revealed two further healed fistulae on the buttocks, posterior to the mid-coronal level. All these findings were compatible with Crohn's disease. Tuberculosis was excluded and she tested negative for HIV. She was found to be HLA-B27 positive and she had persistently raised ALP and γGT. Magnetic resonance cholangiography showed smooth intra-and extra-hepatic bile ducts, a normal gallbladder and no biliary obstruction. The common bile duct (CBD) measured 10 mm, a slight prominence which was of uncertain significance. Primary sclerosing cholangitis could not conclusively be diagnosed on MRC. A liver biopsy was performed. Histology showed an inflammatory infiltrate of lymphocytes, plasma cells and neutrophils. There was portal fibrosis, with typical concentric laminar fibrosis around bile ducts ("onion skinning"). The bile ducts were infiltrated by lymphocytes and showed basement membrane thickening. Some bile ducts appeared atrophic and distorted. The picture was compatible with PSC stage II (9). Azathioprine 100 mg and UDCA 15 mg/kg was started. She tolerated the azathioprine well and the dose was increased to 200 mg per day. The remaining active fistula, at the site of ischiorectal abscess drainage, is progressively draining less and closing. Her liver enzymes have also markedly improved.

Discussion

Until recently, few cases of PSC have been reported in black people. To our knowledge, 10 black patients with classical PSC and IBD have been outlined in four reports world-wide, before 2010 (3,10-12). Two reports from South Africa describe four patients with PSC ; three of them were part of a series describing patients with UC, of whom the gender was not reported ; the fourth patient was a female with Crohn's disease (10,11). One series of African American patients with IBD, reports on three cases of PSC associated with UC, but again without reporting on the gender of the patients (3). A single report from the UK describes three black women with PSC and UC (12). It is notable that in the two reports

specifying the gender, all four patients were female. Only the study from the UK reported on HLA antigens and then only on class II antigens (12). Only one patient out of 10 had Crohn's disease (10). Recently, 815 cases of PSC (60.7% with IBD) in African Americans listed for liver transplantation, in the United States of America (USA), were reported as part of a cohort of genetically diverse patients listed for liver transplantation in the USA (13). This retrospective report spanned a period of 14 years. It is worth noting that there is an estimated 19.6% European admixture in the African American population (14).

Crohn's disease is rare in black South Africans, the estimated incidence being 0.3/100000/year in one report from Cape Town, as opposed to 2.6/100000/year in whites (4). The two cases presented are two of only three black patients with Crohn's disease seen at our unit in the last five years, to the end of 2010. The remaining patient, a young black woman, with no evidence of PSC has a grandparent of European decent. She does not carry HLA-B27. The prevalence of HLA-B27 in black South Africans has been reported to be 0.83% (i.e. $^1/_{120}$) as opposed to 11.6% (i.e. $^1/_9$) among white South Africans (8). As a result, diseases known to be associated with HLA-B27 are uncommon in black people from South Africa (8).

Although the aetiology of PSC is unknown, the association with HLA-B8 and -DR3 and others, is well known (1). The recent genome-wide association study for PSC showed that the HLA association was important, especially with the HLA-B region (1). A specific association between PSC and HLA-B27 has not been reported. Race as an important determinant in the development of PSC, has been suggested in some reports (3,12). Primary Sclerosing Cholangitis was found in a larger proportion of African American patients with UC than in the white population (3). Specifically, in a cohort of patients with UC from the UK, three out of four black people with UC (all women), developed PSC (75%) as opposed to four out of 162 caucasian patients (2.5%) ($p = 0.0002$) (12). It would appear that black people with inflammatory bowel disease have an increased risk of developing PSC, but this requires further study. Gender also seemed to be an important determinant in the latter study, with all black patients with PSC being female (12), whereas symptomatic PSC world-wide has a male predominance. The only other report of PSC in a black person with IBD, where gender was specified, was in a female patient with Crohn's disease (10).

These cases point to an important pathogenetic association. The occurrence of a triad of PSC, Crohn's disease and HLA-B27, in two unrelated black women from different geographical locations (250 km apart), suggests that these findings, in black South Africans, are linked. Crohn's disease and PSC are rare in this population group and HLA-B27 relatively so. Their concurrent presence in two patients, who together form the known cohort of black patients with Crohn's disease in our unit, without evidence of European ancestry, is noteworthy. It may be that the presence of HLA-B27 in black people poses a risk for development of Crohn's disease and PSC, which may be more pronounced in women, suggesting a common pathogenetic role for HLA-B27 in these two related conditions, in South African black women. The pathogenetic role may be similar to the role in other HLA-B27 associated diseases (5). Hypotheses include dendritic cell dysfunction with reduced tolerance to microbial flora, and the formation of cell surface dimers of HLA-B27 heavy chains with resultant immune modulation and inflammation. Antigen presentation is probably not involved. A recent report on a possible link between HLA-B27 misfolding and immune dysregulation, deserves specific mention (5). Activation of the unfolded protein response (UPR) due to HLA-B27 misfolding in HLA-B27/Human β_2-microglobulin transgenic rats, causes activation of the Interleukine-23 (IL-23)/IL-17 axis, expansion of CD4 + memory T cells (Th17 phenotype) in the colon and the development of colitis, in these animals. Initial upregulation of HLA-B27 probably occurs as a result of stimulation of antigen presenting cells with toll-like receptor agonists like lipopolysaccharide (LPS). The UPR resulting from HLA-B27 upregulation and misfolding in activated macrophages causes exaggerated production of IL-23 in response to LPS, stimulating Th17 cells to produce IL-17. Concomitant production of IFNγ may sustain HLA-B27 expression and perpetuate the cycle. While we are not aware of any models supporting involvement of the UPR in the development of PSC, the normal liver is constantly exposed to LPS from the gut (15). Furthermore, biliary epithelial cells, from patients with PSC, have been shown to contain abnormally accumulated LPS (15). Whether the UPR, fuelled by LPS exposure of the liver in some individuals who are HLA-B27 positive, may lead to PSC, deserves further study. As far as we are aware, an association between HLA-B27 and PSC has not been documented, until now.

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